CELL THERAPY MANUFACTURING MARKET 2018-2030

Dissertation submitted in partial fulfillment of the requirement for the degree of

MASTER OF TECHNOLOGY

IN

BIOTECHNOLOGY

By

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UNDER THE GUIDANCE OF

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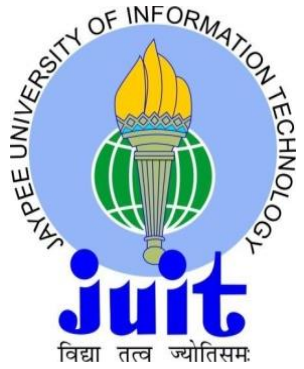

JAYPEE UNIVERSITY OF INFORMATION TECHNOLOGY, WAKNAGHAT
MAY 2018

CERTIFICATE

This is to certify that the work reported in the MTech. Thesis entitled **"Cell Therapy Manufacturing Market 2018-2030"**submitted by **Natasha Thakur** in partial fulfillment for the award of degree of MTech. in Biotechnology from **Jaypee University of Information & Technology, Waknaghat** has been carried out under my supervision. This work has not been submitted partially or wholly to any other University or Institute for the award of any other degree, diploma or such other titles.

Ms. Simriti Gupta
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Roots Analysis Pvt. Ltd.
Date:

DECLARATION

I hereby declare that the work reported in the MTech. thesis entitled **"Cell Therapy Manufacturing Market 2018-2030"**submitted at **Jaypee University of Information Technology, Waknaghat** is an authentic record of my work carried out under the supervision of **Mr. Gaurav Chaudhary** and **Ms. Simriti Gupta**. I have not submitted this work elsewhere for any other degree or diploma.

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Certified that the above statement made by the student is correct to the best of our knowledge and belief. Roots Analysis owns the copyright of the findings presented in this report. Under no circumstances should this information be shared with other third parties without the prior consent of the company.

Ms. Simriti Gupta
Associate
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ACKNOWLEDGEMENT

This project is an outcome of continual work over and intellectual support from numerous sources. Therefore, I would like to express my sincere thanks to the people who have helped me the most throughout my project.

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At last but not the least I am deeply grateful to all the members of Roots Analysis whorendered their help during the course of my training and my parents for their motivation, continual support and encouragement at all the stages of my life.

Natasha Thakur

(133807)

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LIST OF ABBREVIATIONS

ASGCT	American Society of Gene and Cell Therapy
ATMPs	Advanced Therapy Medicinal Products
cGMP	Current Good Manufacturing Practices
ESCs	Embryonic Stem Cells
GRA	Georgia Research Alliance
iPSCs	Induced Pluripotent Stem Cells
KOLs	Key Opinion Leaders
MSCs	Mesenchymal Stem Cells / Mesenchymal Stromal Cells
NCMC	National Cell Manufacturing Consortium
NIST	National Institute of Standards and Technology
NK Cells	Natural Killer Cells
Tregs	Regulatory T-cells

ABSTRACT

The project "*Cell Therapy Manufacturing Market, 2018-2030"* provides an extensive study of the rapidly growing market of cell therapy manufacturing and focuses both on contract manufacturers and cell therapy developers with in-house manufacturing facilities. Cell therapy is based on the premise that the patient's own cells (autologous) or those from a healthy donor (allogeneic) can be programmed to combat certain types of diseases when they are re-infused into the body. These therapies are anticipated to emerge as viable alternatives to conventional treatment options. The scope of this project primarily includes manufacturing of advanced therapy medicinal products (ATMPs) that involve the use of immune cells such as T-cells, Tregs, dendritic cells, tumor cells and NK cells, and stem cells such as adult stem cells, human embryonic stem cells (ESCs) and induced pluripotent stem cells (iPSCs).Several players, including cell therapy developers, research institutes, contract manufacturing organizations, and government and non-profit organizations, are playing a critical role in the development and manufacturing of these cell therapies.

During the course of my on-job training, I worked on different modules of the project. These include the introduction of cell therapy manufacturing, pipeline of several players involved in this field, detailed profiling of those players, information regarding collaborations and partnerships, roadmaps, regulatory landscape, non-profit organizations, primary research and automation in cell therapy manufacturing. Apart from this, I contributed in two additional projects namely, Gene Therapy and Undruggable Cancer Targets where I covered short profiling of companies, worked on different representations and collected KOLs.

CHAPTER 1

COMPANY PROFILE

1.1 Company Overview

Roots Analysis Pvt. Ltd. is a business research and consulting firm, which specializes in providing in-depth business research and consulting services for bio/pharmaceutical industry. Focused on providing an informed and impartial view on key challenges facing the industry, the research is primarily driven by an in-depth analysis covering the following parameters [1]:

- Research and development
- Technology evolution
- Existing market landscape
- Future Commercial potential
- Regulatory concerns
- Regional growth drivers
- Risks and opportunities

The firmhas expertise in analyzing areas that have lacked quality research so far or require more focused understanding within the broader industry. Apart from writing reports on identified areas, the company also provide bespoke research / consulting services dedicated to serve our clients in the best possible way.

The business reports highlight trends ranging from commercial success / potential, technological developments and future outlook built around opportunities and threats.

The company majorly focus on areas spanning the following domains:

- Therapeutic segments
- Emerging technologies
- Medical devices
- Drug Delivery
- Clinical Trials

1.2 Research Methodology

The data presented in the reports has been gathered via secondary and primary research. For all our projects, we conduct interviews with experts in the area (academia, industry, medical practice and other associations) to solicit their opinions on emerging trends in the market. This is primarily useful for us to draw out our own opinion on how the market may evolve across different regions and technology segments. Wherever possible, the available data has been checked for accuracy from multiple sources of information.

The secondary sources of information include:

- Annual reports
- Investor presentations
- SEC filings
- Industry databases
- News releases from company websites
- Government policy documents
- Industry analysts' views

CHAPTER 2

INTRODUCTION

2.1Chapter Overview

Cell-based therapies involve the use of different types of cells for achieving a desired therapeutic benefit. These cells can be immune cells, such as antigen presenting cells (dendritic cells and macrophages), natural killer cells and lymphocytes (T-cells), adult stem cells / tissues (mesenchymal cells, hematopoietic progenitor cells), embryonic stem cells, induced pluripotent stem cells, and other advanced therapy medical products, such as chondrocytes. As the increasing number of cell therapy products progress through various phases of clinical development, the demand for their manufacturing is likely to become stronger in the near future.Cell therapies are based on the premise that the patient's own cells (autologous), or those from a healthy donor (allogeneic), can be genetically re-programmed to combat various diseases. As anticipated, these therapies have emerged as viable alternatives to traditional treatment options, such as small molecule drugs. The last two decades have witnessed a number of advances in cell therapies, particularly in their manufacturing processes. However, even the latest and most promising advances in modern medicine have their own set of challenges and risks, which need to be addressed to ensure continued growth.

Manufacturing of cell therapies is a complex and logistically challenging multi-step process. It involves high capital costs, culturing of cells for several days in regulated environment and management by skilled personnel. Inception of cell therapies has introduced the concept of *one batch run equals to one product*. Currently, for the purpose of manufacturing, cell-based products for clinical trials, companies / academia are utilizing open lab-based systems; however, commercial manufacturing of such therapies demands automated and scalable closed systems as well as robust, reproducible and standardized procedures. Despite multiple challenges related to manufacturing of thesetherapies, several stakeholders, including service providers, are continuously investing in efforts to combat specific roadblocks.

2.2 Cell-Based Therapies: Introduction

The American Society of Gene and Cell Therapy (ASGCT) defines cell therapy as a therapeutic modality that contains either normal or modified cells, which are administered to patients for the treatment of various diseases. In this form of therapy, patients are injected with living and intact human cells that are deemed to provide therapeutic benefit. The transplanted cells have been shown to help in restoring or repairing the function of cells, which are damaged or have ceased functioning due to disease. The main goal of cell therapy is to target the root cause of the disease at the cellular level [2].

2.2.1 Cell-Based Therapies: Classification

The EU regulatory authority provides a system of classification on the basis of the extent of genetic manipulation required for homologous use (such as transplants / transfusions) and heterogeneous use (such as ATMPs) with respect to quality, safety and efficacy of the therapeutic modality. As per the Article (2) (a) of Regulation (EC) No.1394/2007, ATMPs are defined as therapeutic products that can exert pharmacological, immunological or metabolic action to restore, correct or modify physiological functions in order to treat diseases [3].

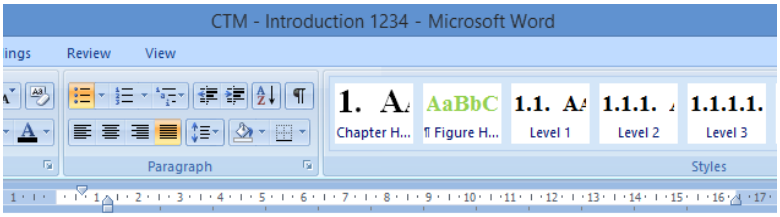
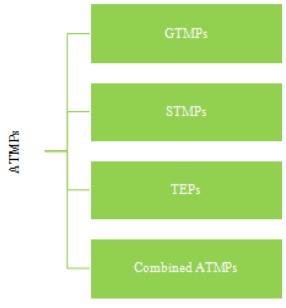


Figure 3.1 **Classification of Advanced Therapy Medicinal Products**

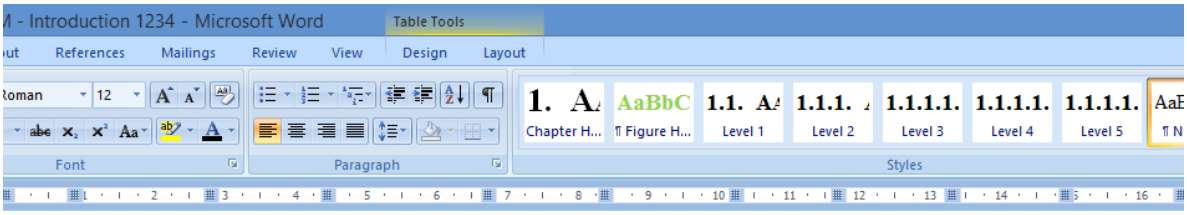


ATMPs: Advanced Therapy Medicinal Products
GTMPs: Genetically Modified Therapy Medicinal Products
STMPs: Somatic Cell Therapy Medicinal Products
TEPs: Tissue Engineered Products

Source: Roots Analysis

Figure 2.1 Highlights the different classes of ATMPs

2.2.2 Cell-Based Therapies: Current Market Landscape



S. No	Name of the Product	Approval Year	Type of Cells Used	Type of Therapy	Indication	Marketed	Company	Manufacturing Location	Manufacturer Type
1	Kymriah[13](tisagenlecleucel)	2017	CAR positive T-cells	Autologous	B-cell precursor acute lymphoblastic leukemia	US, EU	Novartis Pharmaceuticals	US	In-house
2	Yescarta[14] (axicabtagenciloleucel)	2017	T-cells	Autologous	B-cell lymphoma	US, EU	Kite Pharma (a Gilead company)	US	In-house
3	Strimvelis	2016	CD34+bone marrow HSCs	Autologous	ADA-SCID	EU	GlaxoSmith Kline	Italy	Contract
4	Zalmoxis[15]	2016[16]	T-cells	Allogeneic	High risk hematological cancers	EU	MolMed	Italy	In-house
5	HeartSheet[17]	2015	Skeletal myoblasts	Autologous	Heart failure	Japan	Terumo	Japan	In-house

Figure 2.2 Represents cell-based therapies that have been approved / launched across different countries

2.3 Cell Therapy Manufacturing: An Introduction

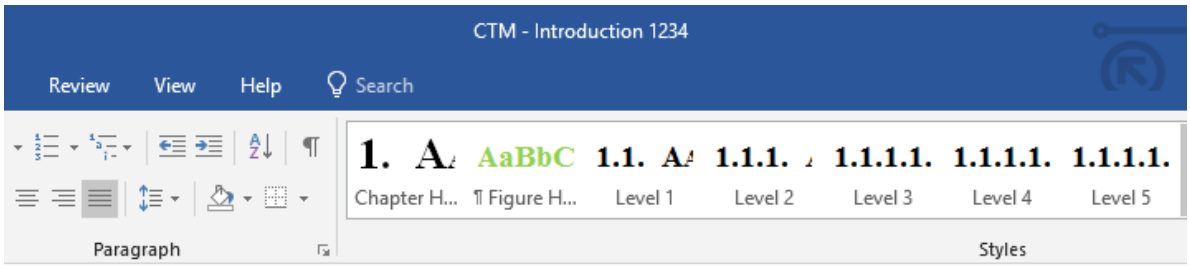
Manufacturing biologics and cell therapies is considerably complex as compared to small molecule drugs. The production of biological products as therapeutic interventions is likely to be influenced by several factors.More specifically, the major considerations that need to be addressed for manufacturing cell therapies are listed below:

- Ethical consent and clearance
- Identification of scalable approaches for separation and purification
- Development and optimization of cost-effective and chemically modified media
- Establishment of closed automated systems for manufacturing of cell therapies for multiple patients at the same time

2.3.1 Cell Therapy Manufacturing: Manufacturing Models

There are two types of manufacturing models:

- Centralized Manufacturing Model
- Decentralized Manufacturing Model



1.4.1. CENTRALIZED MANUFACTURING MODEL

The concept of manufacturing the pharmaceutical products through conventional methodologies follow the centralized manufacturing approach. Most of the allogeneic cell therapies in development phase implement centralized manufacturing model which consists of a single facility where the process of production and distribution of therapeutic products are carried out simultaneously. According to a non-profit organization (APQC), companies following centralized approach of manufacturing are in benefit as they have profit of about 3% in the manufacturing cost as compared to the decentralized companies.[40,41]

Figure 3.3 represents the sequential steps followed in the centralized manufacturing approach.

Figure 3.3 **Centralized Manufacturing: Process Model**

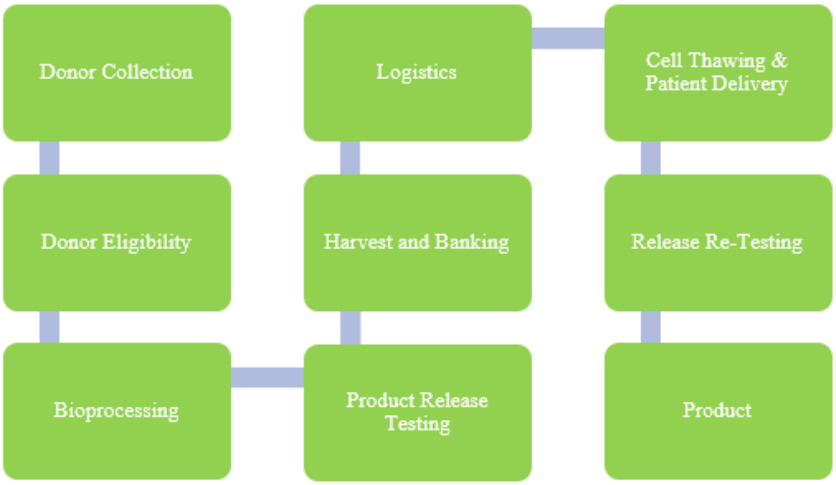
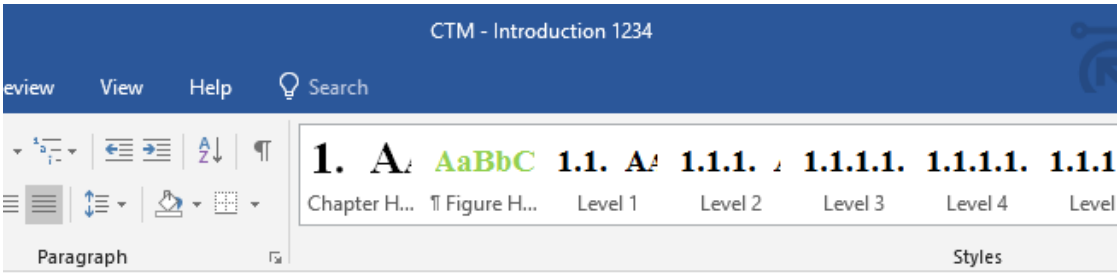


Figure 2.3 Represents the process model for centralized manufacturing



1.4.2. DECENTRALIZED MANUFACTURING MODEL

Decentralized model offers its platform of manufacturing to those health care therapies that have high degree of personalization. Autologous or personalized cell therapy demands a scale-out approach in order to make sure that the patient material is completely isolated and is prevented from cross contamination. Decentralized manufacturing, also known as, redistributed manufacturing turned the cell therapy manufacturing approach upside down by overcoming the major challenge of distribution of high volume goods. This approach split their production processes across different locations, sites and geographic regions. Decentralized model of manufacturing imposes significant changes in the organizational structure, bringing out the hidden challenges that must be addressed. [43,44] Figure 3.4 represents the process model of decentralized manufacturing approach.

Figure 3.4 **Decentralized Manufacturing: Process Model**

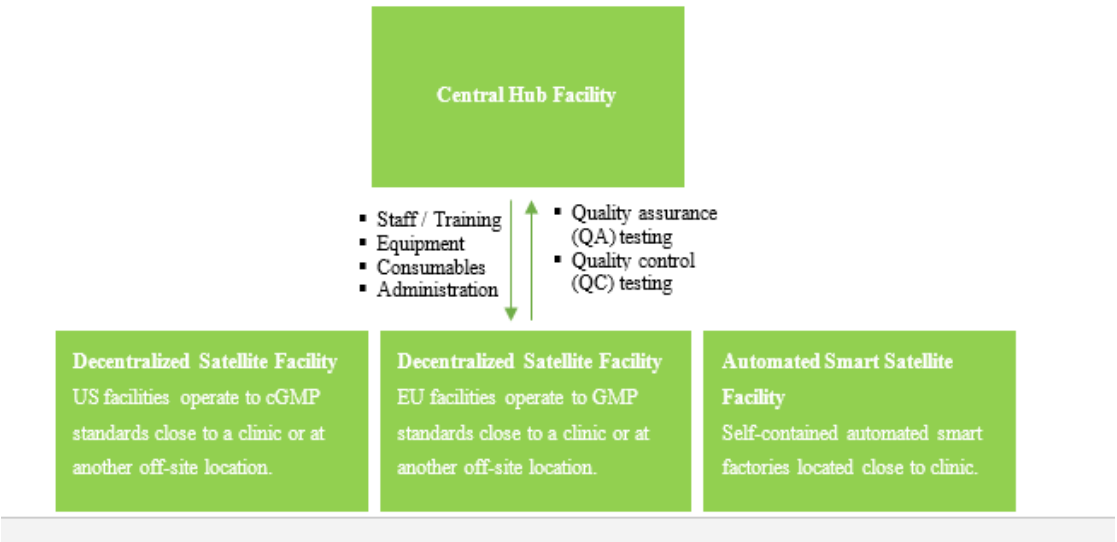


Figure 2.4 Represents the process model for decentralized manufacturing

2.3.2 Cell Therapy Manufacturing: Types of manufacturers

Most cell therapy developers prefer to collaborate with contract manufacturers and outsource their manufacturing requirements. At the same time, larger and more established firms choose to invest in developing in-house manufacturing capabilities. Despite the exorbitant costs, the unavoidable need for elaborate manufacturing facilities, stringent regulatory scenario and other drawbacks, there is a growing interest in this emerging field, and a number of companies have recently stepped in.

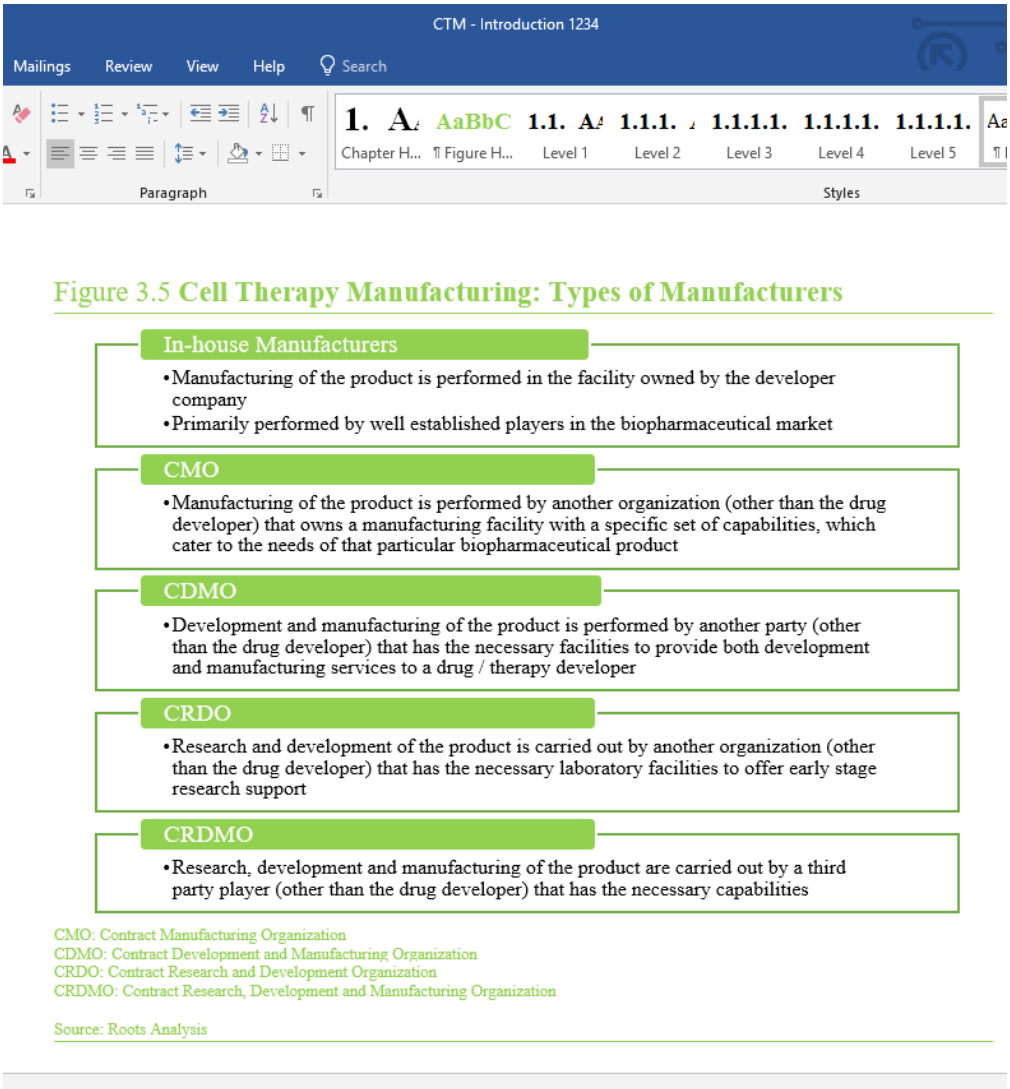


Figure 2.5 Represents the types of manufacturers involved in cell therapy manufacturing

2.4 Cell-Based Therapies: Key Manufacturing Challenges

Some of the key challenges faced by cell therapy manufacturers are [4]:

- Sophisticated equipment is required for the relocation, transport and multi-site distribution of cell therapy products. Therefore, the facilities where cell-based therapies are to be developed and manufactured should be established at easily accessible locations, such as near airports for overseas transitions.
- Setting up cGMP facilities and obtaining the necessary qualifications and certifications is not only challenging, but also requires heavy investments. Moreover, cell production facilities should also be equipped with proper storage rooms, clean rooms, cryopreservation rooms and have various other cell processing capabilities as well.
- Contamination is a key concern when it comes to manufacturing cell therapy products. To overcome this, manufacturers are required to modify their current procedures to incorporate closed manufacturing systems.

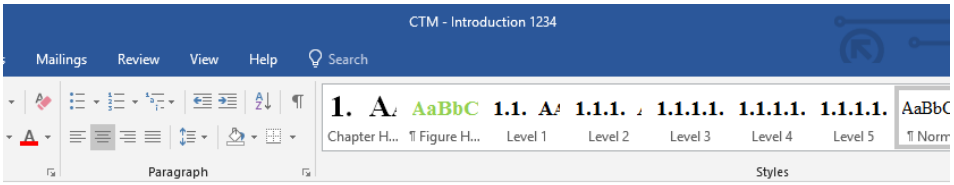
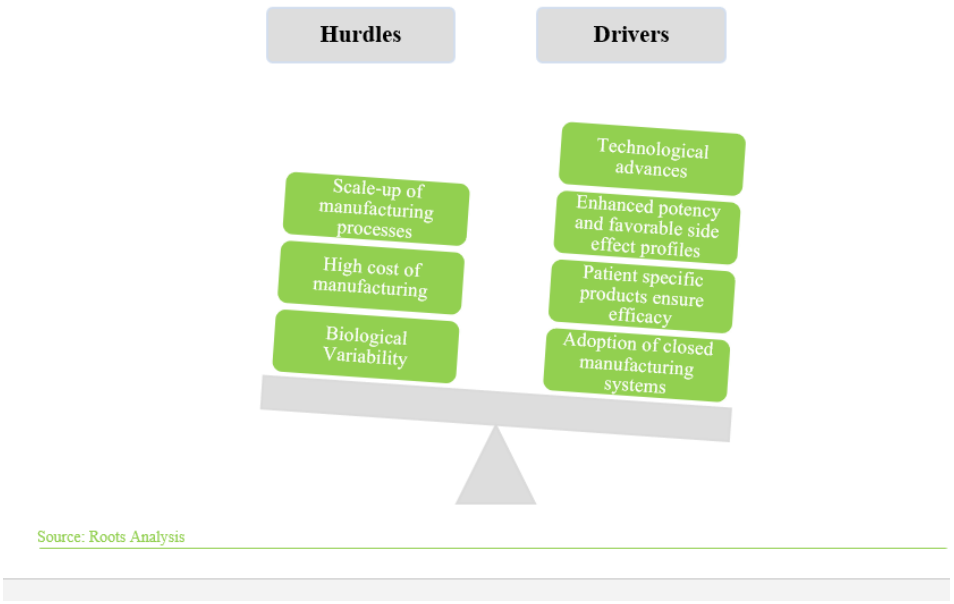


Figure 3.6 highlights the major roadblocks and key growth drivers of the cell therapy market.

Figure 3.6 **Cell Therapy: Challenges and Drivers**



Source: Roots Analysis

Figure 2.6 Highlights the major roadblocks and key growth drivers of the cell therapy market

CHAPTER 3

MARKET OVERVIEW

3.1Chapter Overview

The use of live cells for therapeutic purposes can be traced back to 1968, when patients were first successfully treated with allogeneic human hematopoietic stem cell transplants. This practice has now become an integral part of clinical procedures in the space of bone marrow regeneration. However, two decades later, the true potential of stem cells remained untapped until stem cells were tested for their use as therapeutic agents for regenerating skeletal tissues. Prochymal, aMSC therapy developed by Osiris Therapeutics, was amongst the first cellular therapies to be approved in Canada and New Zealand [5].

3.2 Overall Market Landscape

Cell therapies have shown positive clinical results and potential to treat life threatening diseases, such as cancer, autoimmune disorders and infectious diseases. Such benefits have outweighed the drawbacks associated with the domain that primarily comprise complex, time consuming and tedious manufacturing processes. This domain has attracted several research institutes and companies to invest time and money. In order to meet the growing demand of increased number of clinical trials and improve the manufacturing processes, more and more organizations are contributing to the space by setting-up capabilities to manufacture cell-based therapies. In this project, we identified over several organizations, including industry stakeholders and academic players that are actively involved in the production of cellular therapies.

3.3Database Building

Database is a list of companies / devices / technologies that has been created from multiple sources including public records, surveys, primary research, and company sources.It serves as the most important stepin the process of report writing. Hence, it must be robust, exhaustive and finely structured.

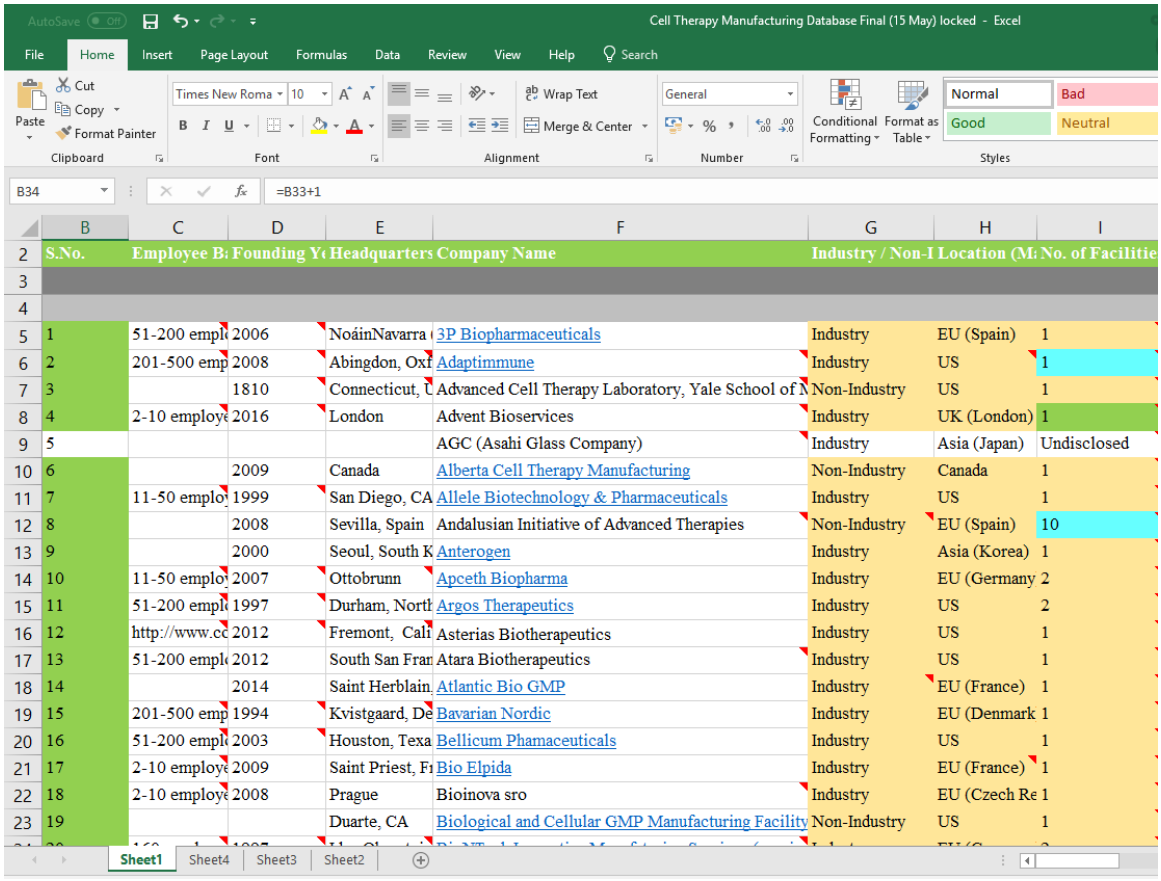
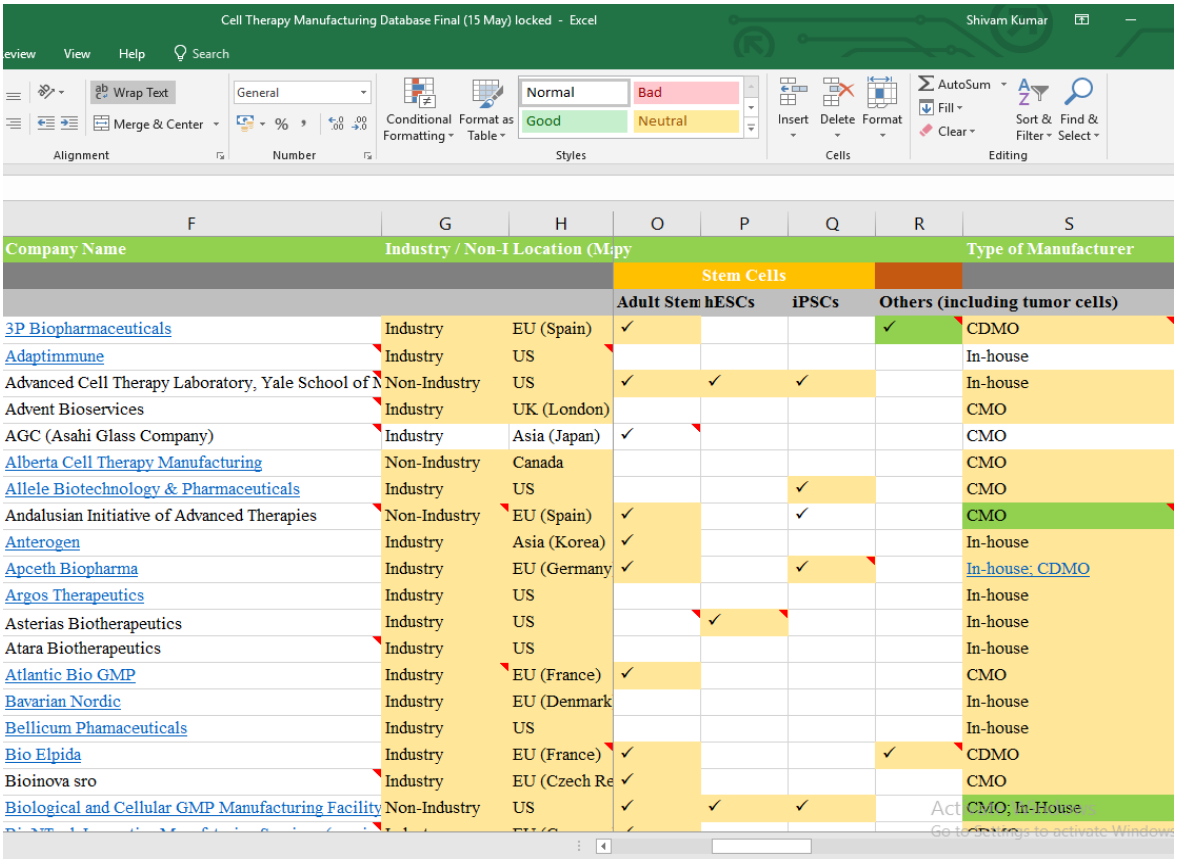


Figure 3.1 Represents the database of the cell therapy manufacturing market

For building a database, several parameters were selected in with respect to the scope of the project. Cell therapy manufacturing market is a service-based project, hence all the industry, non-industry players involved in manufacturing of cell therapies were captured along with some of the basic information about the organization. For example, the founding year of the company, total number of employees in the company and their headquarters. Other key parameters that were captured in the project are listed below:

- Type of organization (industry / non-industry player)
- Location of the manufacturing facility
- Total number of manufacturing facilities
- Type of cells the company is manufacturing
- Type of manufacturer
- GMP-complaint
- Scale of operation



F	G	H	O	P	Q	R	S
Company Name	Industry / Non-I	Location (Mapy					Type of Manufacturer
			Stem Cells				
			Adult Stem	hESCs	iPSCs	Others (including tumor cells)	
3P Biopharmaceuticals	Industry	EU (Spain)	✓			✓	CDMO
Adaptimmune	Industry	US					In-house
Advanced Cell Therapy Laboratory, Yale School of M	Non-Industry	US	✓	✓	✓		In-house
Advent Bioservices	Industry	UK (London)					CMO
AGC (Asahi Glass Company)	Industry	Asia (Japan)	✓				CMO
Alberta Cell Therapy Manufacturing	Non-Industry	Canada					CMO
Allele Biotechnology & Pharmaceuticals	Industry	US			✓		CMO
Andalusian Initiative of Advanced Therapies	Non-Industry	EU (Spain)	✓		✓		CMO
Anterogen	Industry	Asia (Korea)	✓				In-house
Apceth Biopharma	Industry	EU (Germany	✓		✓		In-house; CDMO
Argos Therapeutics	Industry	US					In-house
Asterias Biotherapeutics	Industry	US		✓			In-house
Atara Biotherapeutics	Industry	US					In-house
Atlantic Bio GMP	Industry	EU (France)	✓				CMO
Bavarian Nordic	Industry	EU (Denmark					In-house
Bellicum Phamaceuticals	Industry	US					In-house
Bio Elpida	Industry	EU (France)	✓			✓	CDMO
Bioinova sro	Industry	EU (Czech Re	✓				CMO
Biological and Cellular GMP Manufacturing Facility	Non-Industry	US	✓	✓	✓		CMO; In-House

Figure 3.2 Provides information on the various parameters captured in the database

CHAPTER 4

ROADMAPS: STRATEGIES TO OVERCOME EXISTING CHALLENGES

4.1Chapter Overview

Cellular therapies, such as T-cell immunotherapies, dendritic cell vaccines and stem cell-based therapies, have evolved considerably over the past few years. Although some of these therapies have been approved in different regions of the world, there are certain challenges that need to be worked on in order to realize their full potential. For this, different organizations have developed comprehensive roadmaps, predicting the anticipated movement of these therapies from clinical trials to commercial launch. Such roadmaps differ for different geographiesand highlight the role of different stakeholders in the industry, such as pharmaceutical companies, academic institutions and government agencies, and their involvement in building a seamless process flow related to the development, production and launch of these therapies.

In my project, we have included roadmap for three geographies:

- Roadmap for the United States
- Roadmap for Europe
- Roadmap for Asia Pacific

4.2Roadmap for the US

In February 2016, the National Cell Manufacturing Consortium (NCMC), the Georgia Research Alliance (GRA) and the Georgia Institute of Technology (Georgia Tech) published a roadmap that identified the challenges associated with cell therapy manufacturing. A revised version of these strategies was published in July 2017 with the support of National Institute of Standards and Technology (NIST). The roadmap highlighted possible strategies, which, if implemented in the coming 10 years, are likely

to facilitate large scale, cost-effective and reproducible manufacturing of high quality cells [6].

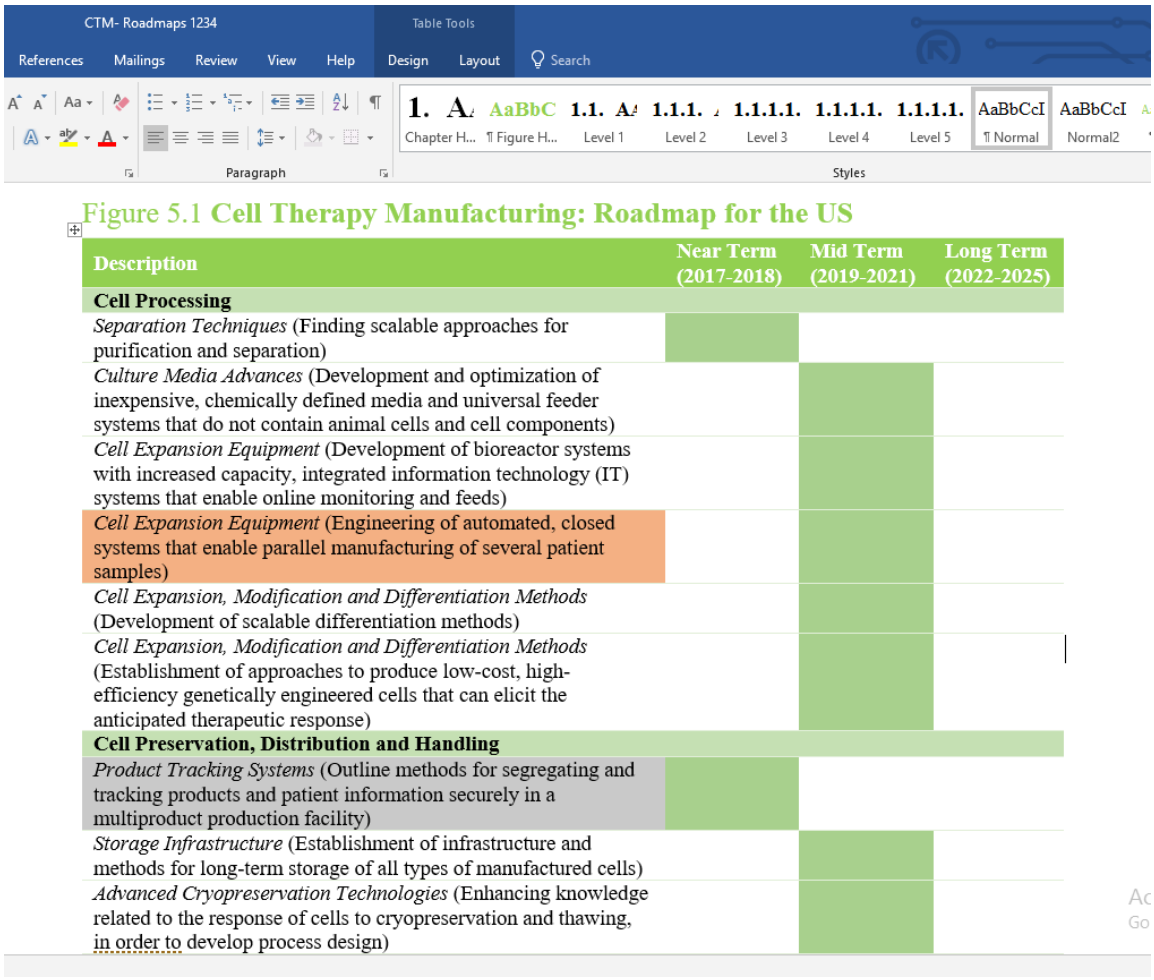


Figure 5.1 **Cell Therapy Manufacturing: Roadmap for the US**

Description	Near Term (2017-2018)	Mid Term (2019-2021)	Long Term (2022-2025)
Cell Processing			
Separation Techniques (Finding scalable approaches for purification and separation)			
Culture Media Advances (Development and optimization of inexpensive, chemically defined media and universal feeder systems that do not contain animal cells and cell components)			
Cell Expansion Equipment (Development of bioreactor systems with increased capacity, integrated information technology (IT) systems that enable online monitoring and feeds)			
Cell Expansion Equipment (Engineering of automated, closed systems that enable parallel manufacturing of several patient samples)			
Cell Expansion, Modification and Differentiation Methods (Development of scalable differentiation methods)			
Cell Expansion, Modification and Differentiation Methods (Establishment of approaches to produce low-cost, high-efficiency genetically engineered cells that can elicit the anticipated therapeutic response)			
Cell Preservation, Distribution and Handling			
Product Tracking Systems (Outline methods for segregating and tracking products and patient information securely in a multiproduct production facility)			
Storage Infrastructure (Establishment of infrastructure and methods for long-term storage of all types of manufactured cells)			
Advanced Cryopreservation Technologies (Enhancing knowledge related to the response of cells to cryopreservation and thawing, in order to develop process design)			

Figure 4.1 Represents the roadmap designed for the United States

4.3 Roadmap for Europe

In November 2016, an Advanced Therapies Manufacturing Action Plan was published by the Medicines Manufacturing Industry Partnerships with recommendations to progress the manufacturing initiatives related to ATMPs in the UK. The roadmap was designed to improve and increase the economic aspect within the healthcare segment. The key takeaways from the roadmap include strengthening and securing a competitive international landscape to captivate investment and applying a simple engagement process to target and seize international mobile investments [7].

4.4 Roadmap for Asia Pacific

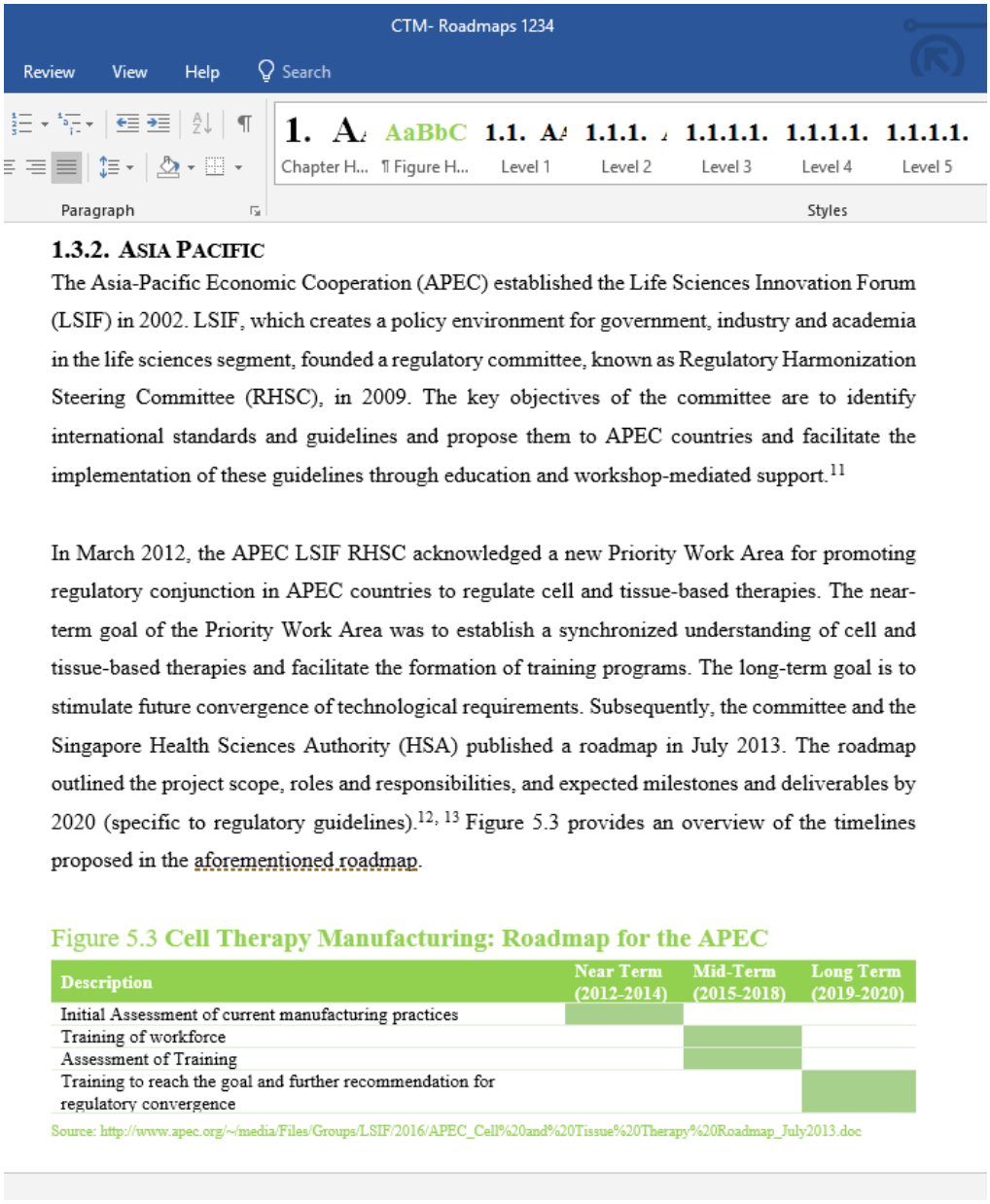


Figure 4.2 Represents the roadmap designed for Asia Pacific

CHAPTER 5

INDUSTRY PLAYERS

5.1Chapter Overview

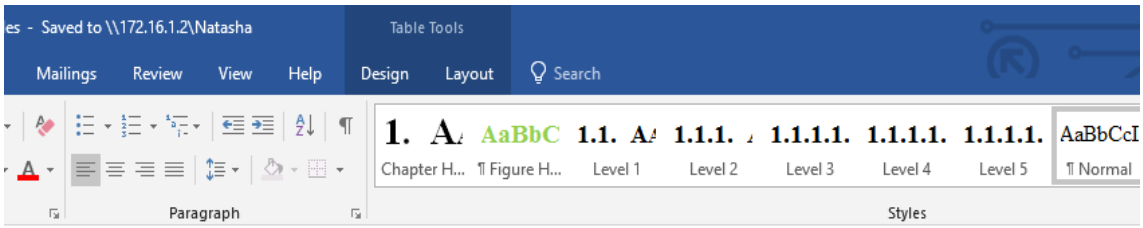
The chapter comprises of detailed profiles of companies that offer services for the development and manufacturing of cell therapies.We have focused primarily on the companies offer a well-established suite of services including product development and manufacturing. In addition, these players have significantly contributed in the advancement of cell therapies by collaborating with other stakeholders in the industry. Each profile includes information on the key features of the facilities, area / infrastructure, regulatory licenses and partnerships inked by the contract manufacturers.

The following companies have been profiled in this project:

- Nikon Cell Innovation
- Cell Therapies
- Cryosite
- Cognate BioServices
- MaSTherCell
- Japan Tissue Engineering (J-TEC)
- Medinet
- KBI Biopharma
- BioNTech Innovative Manufacturing Services
- Fujifilm Cellular Dynamics
- Brammer Bio
- WuXi Advanced Therapies
- Cell and Gene Therapy Catapult
- CELL*for*CURE
- Lonza
- PCT, A Hitachi Group Company
- Roslin Cells Therapies

- Waisman Biomanufacturing

5.2Example of an Industry Profile: Cell and Gene Therapy Catapult



The company was founded in 2012 with the vision to develop, deliver and commercialize scientific methodologies to bridge the gaps in manufacturing cell and gene therapy products. The company aims to advance cell therapy products in clinical studies in order to limit risks associated with further investment. According to the company, this can be achieved by providing technical expertise and infrastructure for manufacturing cell and gene therapy products. The company also offers services for guidance on regulatory issues to ensure the safe entry of products in clinical trials, and also provides platform for facilitating global collaborations. The company was renamed as Cell and Gene Therapy Catapult in February 2016.[3]

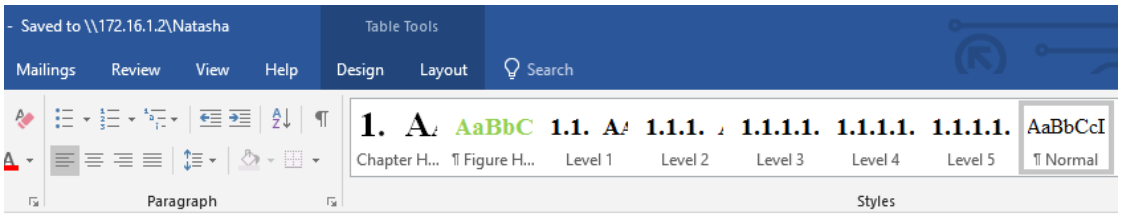
Table 7.1 provides a brief overview of Cell and Gene Therapy Catapult.

Table 7.1 **Cell and Gene Therapy Catapult: Company Overview**

Key Parameters	Description
Headquarters	London, UK
Year of Establishment	2012[4]
Number of Employees	More than 130[5]
Services	▪ Product development ▪ Process development ▪ Commercial / clinical manufacturing ▪ Clinical and regulatory support
Manufacturing Site(s)	Guy's Hospital (viral vector lab) and Stevenage, UK[6]

Source: Roots Analysis

Figure 5.1 Represents the company overview section in an industry profile



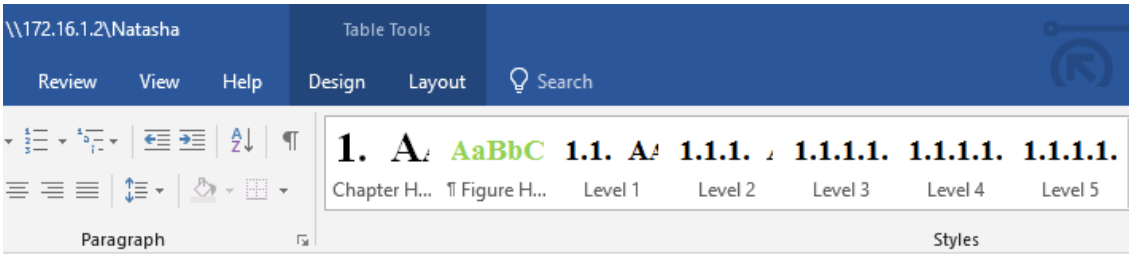
1.2.2. SERVICE PORTFOLIO

The firm provides a wide range of services, which include R&D services, contract research, product development and manufacturing, and process development. Figure 7.1 provides a pictorial representation of the services offered by Cell and Gene Therapy Catapult.

Figure 7.1 **Cell and Gene Therapy Catapult: Services**

Source: Company's Website

Figure 5.2 Represents the service portfolio section in an industry profile



1.2.3. MANUFACTURING CAPABILITIES

Cell and Gene Therapy Catapult expects to open its fully functional, large-scale GMP manufacturing facility located within the Stevenage Bioscience Catalyst campus in 2017.[12] Stevenage Bioscience Catalyst was established as a joint venture between the Department for Business Innovation and Skills, GSK, the Wellcome Trust and Innovate UK. The facility is considered to be amongst the first few GMP compliant production plants in the UK that provides translational research and development services to pharmaceutical and biotechnology companies.[13] The GBP 55 million, large-scale GMP cell therapy manufacturing center of Cell and Gene Therapy Catapult is focused on catering to the development needs of late stage clinical candidates. According to the company, the center is likely to support the manufacturing agreement that was recently signed with Cellular Therapeutics for the development of immune cell therapy clinical program.[14] The facility offers space on lease for use to the cell and gene therapy players. This center is likely to offer capabilities for manufacturing products for late-stage clinical studies and for commercialization.

Table 7.2 provides additional details on Cell and Gene Therapy Catapult's facility.

Table 7.2 **Cell and Gene Therapy Catapult: Overview of Manufacturing Capabilities**

Key Features	Stevenage Facility
Year of Founding	2015[15]
Location	Stevenage Bioscience Catalyst, UK[16]
cGMP / GTP compliant	Yes
Services	▪ Process development ▪ Product development and manufacturing
Scale of Operation	Clinical, Commercial
Controlled Environment Rooms (CERs)	Yes
Type of Cells	Autologous and allogenic cells

Figure 5.3 Represents the manufacturing capabilities section in an industry profile

CHAPTER 6

NON-INDUSTRY PLAYERS

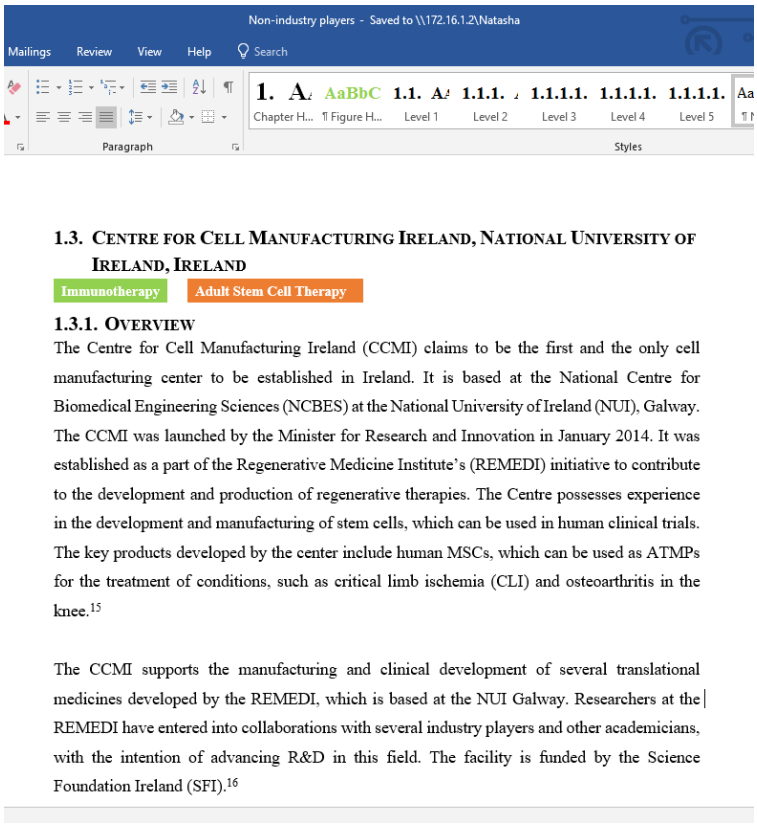
6.1Chapter Overview

There area number of academic players that areactively involved in the field of cell therapy manufacturing. Apart from making generous contributions, in the form of grants, many non-industry players have extended their support as contract manufacturers as well. The chapter comprises of details of the various facilities established by academic players to provide support (for in house requirements and to other players) in clinical and commercial manufacturing of cell-based therapeutics. Each profile comprises of an overview of the institute / organization, along with a list of key features of its facilities and capabilities, covering information such as its area, infrastructure, regulatory licenses / certifications, equipment used, and its product and / or service portfolio.

The following cell therapy manufacturing facilities have been profiled for this project:

- Center for Cell and Gene Therapy, Baylor College of Medicine, US
- Center of Cell Manufacturing Ireland, National University of Ireland, Ireland
- Clinical Cell and Vaccine Production Facility, University of Pennsylvania, US
- Guy's and St. Thomas GMP Facility, Guy's Hospital, UK
- Laboratory of Cell and Gene Medicine, Stanford University, US
- Molecular and Cellular Therapeutics, University of Minnesota, US
- Newcastle Cellular Therapies Facility, Newcastle University, UK
- Rayne Cell Therapy Suite, King's College London, UK
- Scottish National Blood Transfusion Service, Scottish Centre of Regenerative Medicine, UK
- Sydney Cell and Gene Therapy, Australia

6.2 Example of a Non-Industry Profile: Center of Cell Manufacturing Ireland, National University of Ireland



1.3. Centre for Cell Manufacturing Ireland, National University of Ireland, Ireland

Immunotherapy | Adult Stem Cell Therapy

1.3.1. Overview

The Centre for Cell Manufacturing Ireland (CCMI) claims to be the first and the only cell manufacturing center to be established in Ireland. It is based at the National Centre for Biomedical Engineering Sciences (NCBES) at the National University of Ireland (NUI), Galway. The CCMI was launched by the Minister for Research and Innovation in January 2014. It was established as a part of the Regenerative Medicine Institute's (REMEDI) initiative to contribute to the development and production of regenerative therapies. The Centre possesses experience in the development and manufacturing of stem cells, which can be used in human clinical trials. The key products developed by the center include human MSCs, which can be used as ATMPs for the treatment of conditions, such as critical limb ischemia (CLI) and osteoarthritis in the knee.[15]

The CCMI supports the manufacturing and clinical development of several translational medicines developed by the REMEDI, which is based at the NUI Galway. Researchers at the REMEDI have entered into collaborations with several industry players and other academicians, with the intention of advancing R&D in this field. The facility is funded by the Science Foundation Ireland (SFI).[16]

Figure 6.1 Represents the overview section in a non-industry profile

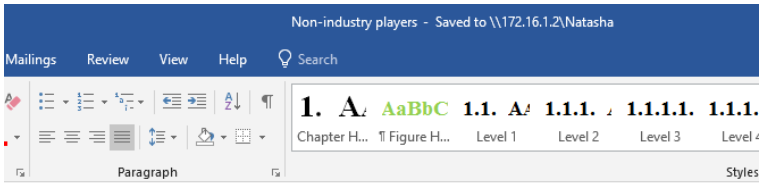


Figure 8.3 **Center for Cell Manufacturing Ireland: Service Portfolio**

Source: Institute Website

Figure 6.2 Represents the service portfolio section in a non-industry profile

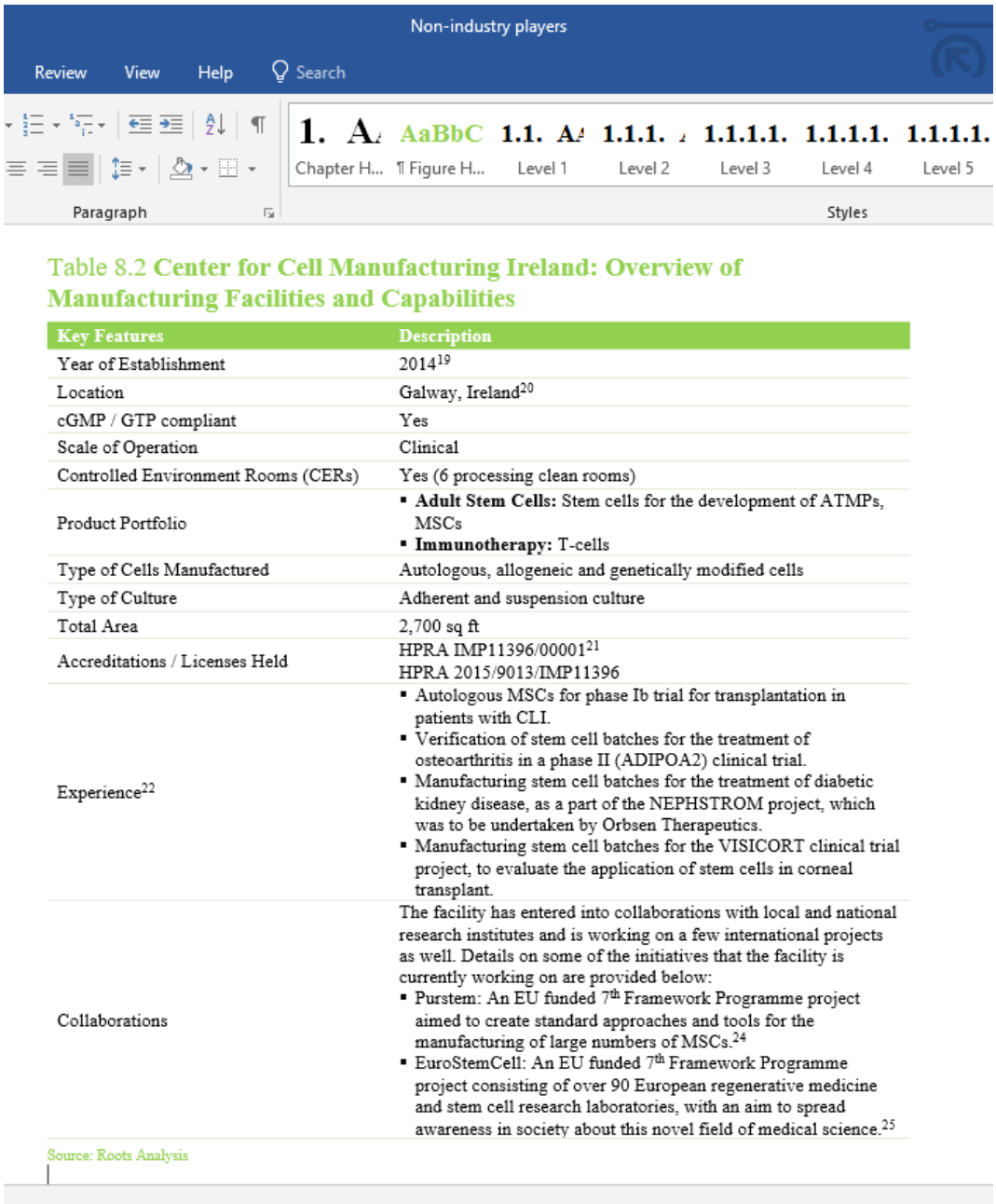


Table 8.2 **Center for Cell Manufacturing Ireland: Overview of Manufacturing Facilities and Capabilities**

Key Features	Description
Year of Establishment	2014[19]
Location	Galway, Ireland[20]
cGMP / GTP compliant	Yes
Scale of Operation	Clinical
Controlled Environment Rooms (CERs)	Yes (6 processing clean rooms)
Product Portfolio	▪ **Adult Stem Cells:** Stem cells for the development of ATMPs, MSCs ▪ **Immunotherapy:** T-cells
Type of Cells Manufactured	Autologous, allogeneic and genetically modified cells
Type of Culture	Adherent and suspension culture
Total Area	2,700 sq ft
Accreditations / Licenses Held	HPRA IMP11396/00001[21] HPRA 2015/9013/IMP11396
Experience[22]	▪ Autologous MSCs for phase Ib trial for transplantation in patients with CLI. ▪ Verification of stem cell batches for the treatment of osteoarthritis in a phase II (ADIPOA2) clinical trial. ▪ Manufacturing stem cell batches for the treatment of diabetic kidney disease, as a part of the NEPHSTROM project, which was to be undertaken by Orbsen Therapeutics. ▪ Manufacturing stem cell batches for the VISICORT clinical trial project, to evaluate the application of stem cells in corneal transplant.
Collaborations	The facility has entered into collaborations with local and national research institutes and is working on a few international projects as well. Details on some of the initiatives that the facility is currently working on are provided below: ▪ Purstem: An EU funded 7th Framework Programme project aimed to create standard approaches and tools for the manufacturing of large numbers of MSCs.[24] ▪ EuroStemCell: An EU funded 7th Framework Programme project consisting of over 90 European regenerative medicine and stem cell research laboratories, with an aim to spread awareness in society about this novel field of medical science.[25]

Source: Roots Analysis

Figure 6.3 Represents the manufacturing capabilities section in a non-industry profile

CHAPTER 7

NON-PROFIT ORGANIZATIONS

7.1Chapter Overview

Several non-profit organizations, academic research centers and other industrial players have continuously supported the development of cell-based therapies in a number of ways. These include funding, assistance in transition to the clinical stage by offering manufacturing services and regulatory guidance. The support from these non-profit organizations has contributed significantly to the growth in the field of cell-based therapies.

7.2Non-Profit Organizations

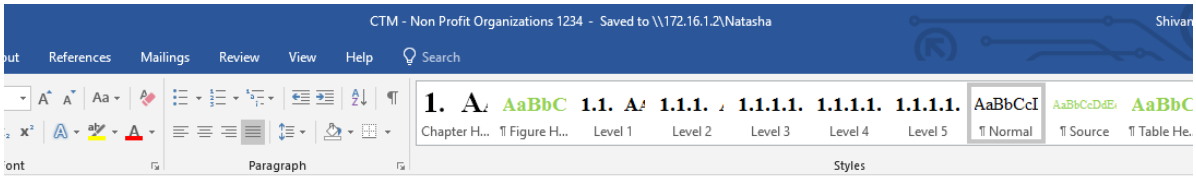


Table 9.1 **Cell Therapy Manufacturing: List of Non-Profit Organizations**[8, 9]

S. No	Organization	Year of Founding	Country	Details
1	Foundation of Croatian Association for Regenerative Medicine and Stem Cell Therapy	2015	Croatia	The organization provides a platform to professionals from different fields who share a common interest towards the advancement of regenerative medicine / stem cell therapies.[10]
2	CellCAN	2014	Canada	It is a network that provides cell therapy manufacturing facilities and services. It also provides a platform for the general public to share knowledge and queries related to regenerative medicine and cellular therapies.[11]
3	European Bank for induced pluripotent Stem Cells (EBiSC)	2014	UK	The Bank provides access to quality-controlled, research-grade iPSC lines, data and cell related services to researchers and industry players, worldwide.[12]
4	National Cell Manufacturing Consortium (NCMC)	2014	US	The NCMC develops and implements technologies that can enable large-scale, cost-effective manufacturing of cell-based therapies by leveraging currently available technologies and processes in a planned manner.[13]

Figure 7.1 Represents the list of non-profit organizations

7.3Example of a Non-Profit Organization:CellCAN

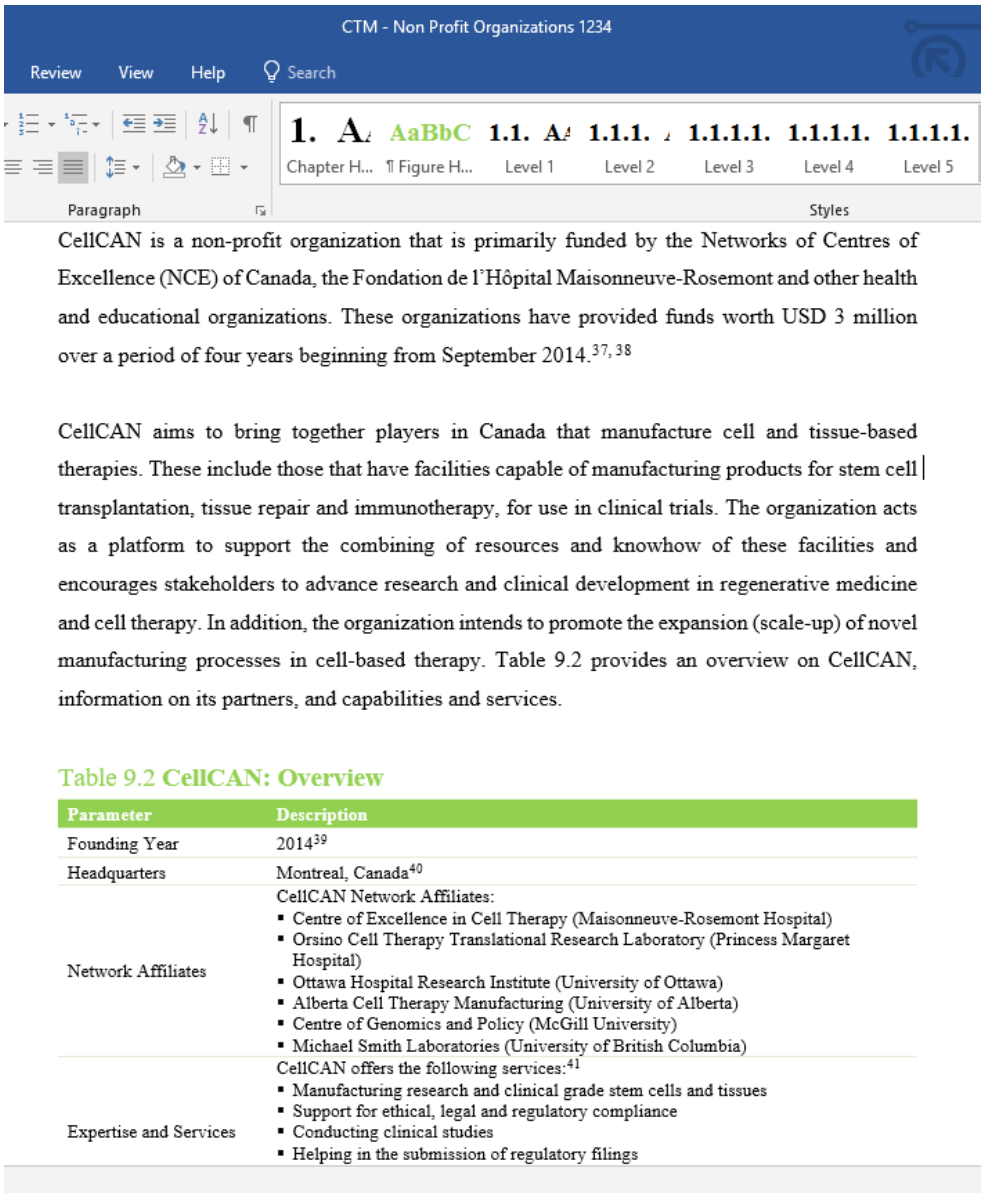


Figure 7.2 Represents an overview of a Non-Profit Organization: CellCAN

7.4International Societies

In addition to non-profit organizations, a number of other organizations / societies have made significant contributions to the field of cell-based therapy. These societies have helped in accelerating the growth in this domain by promoting these novel therapies, spreading awareness and providing platforms for researchers, clinicians and other

stakeholders in the industry to come together to discuss future opportunities, therapeutic and commercial potential, and the challenges associated with this field.

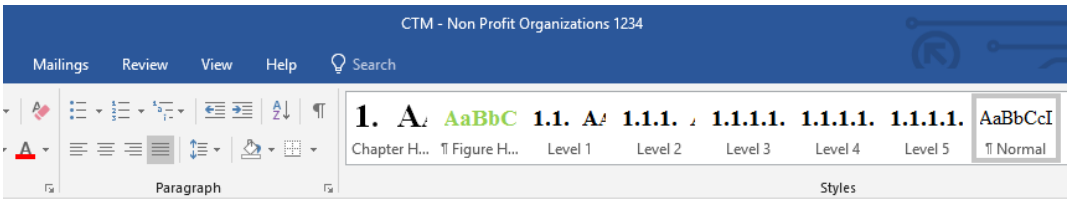


Table 9.6 **Cell Therapy Manufacturing: List of Gene and Cell Therapy Societies**

S. No.	Organization / Society
1	American Society of Gene and Cell Therapy
2	Australasian Gene and Cell Therapy Society
3	Austrian Network for Gene Therapy
4	British Society of Gene Therapy
5	European Society of Gene and Cell Therapy
6	Finnish Gene Therapy Society
7	French Society of Cellular and Gene Therapy
8	German Gene Therapy Society
9	International Society for Cancer Gene Therapy
10	Irish Society for Gene and Cell Therapy
11	Israeli Society for Gene and Cell Therapy
12	Japan Society for Gene Therapy
13	Korean Society of Gene and Cell Therapy
14	The Netherlands Society of Gene and Cell Therapy
15	Spanish Society of Gene and Cell Therapy
16	Swedish Society for Gene and Cell Therapy
17	Turkish Society for Gene and Cell Therapy

Source: http://www.genetherapynet.com/societies.html

Figure 7.3 Represents the list of various international gene and cell therapy societies

CHAPTER 8

REGULATORY LANDSCAPE

8.1Chapter Overview

The manufacturing of advanced therapies, such as cell-based therapies and cellular products, is complex and there are a number of challenges associated with their transition from the laboratory to the clinics. Manufacturing facilities and production protocols designed for such product candidates need to undergo strict regulatory checks and comply with stringent standards.

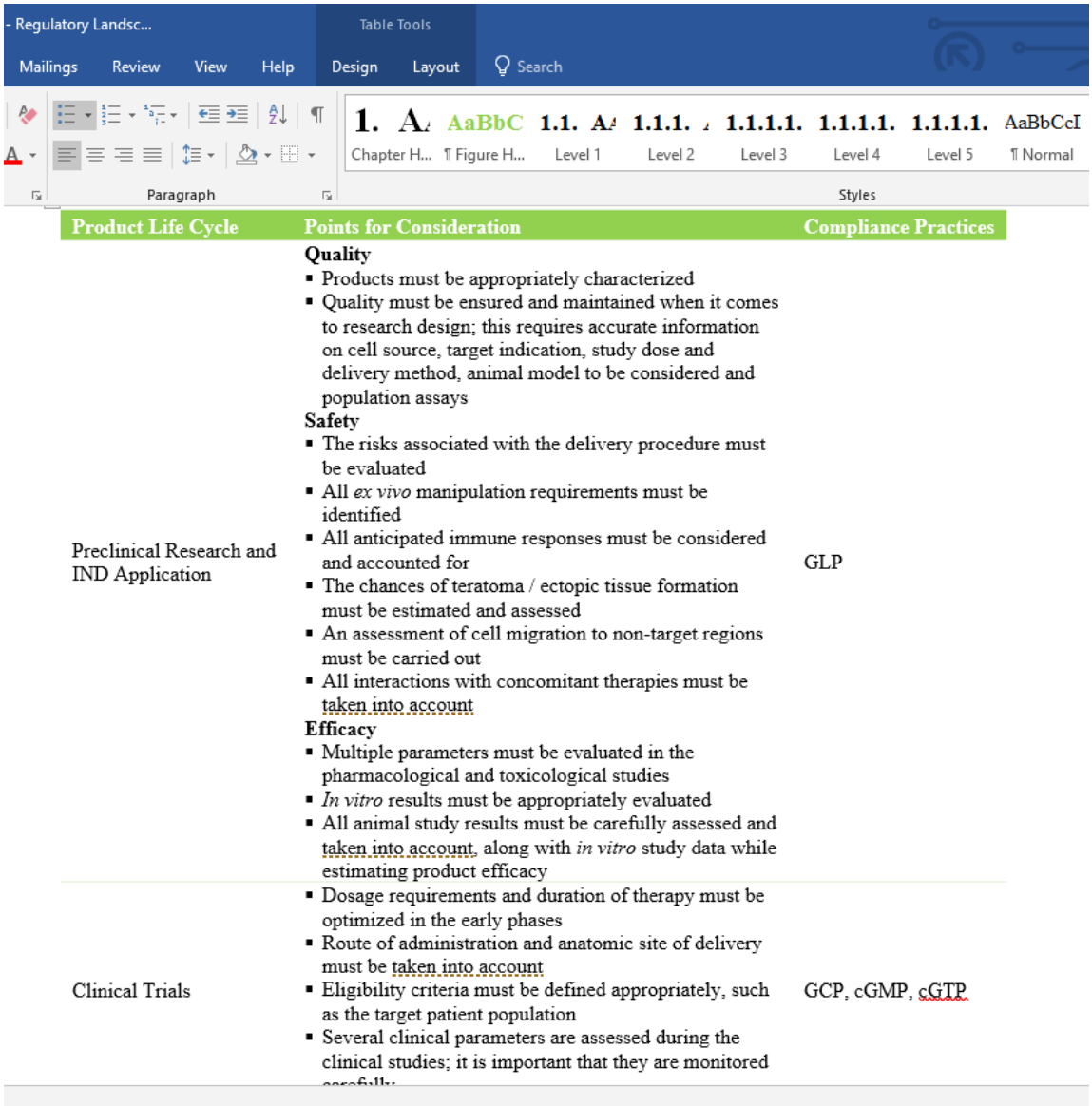
The chapter provides a brief background on the current scenario with respect to regulatory guidelines for the cell therapies. Further, it discusses the challenges related to regulations and finally provides details on the regulatory guidelines for different phases of development.

8.2Regulatory Systems

Although various regulatory bodies across the globe agree in terms of product safety and quality, there are aspects in which they differ in opinions as well, such as definition / classification of products.Such differences in various geographies make it difficult for cell therapy developers to move from one geographical region to another.

We have also discussed some key attributes with respect to regulatory landscape in cell therapy manufacturing market. It includes:

- Regulatory system in US
- Regulatory system in Europe
- Regulatory system in Japan
- Conditional Approval
- Accreditations in cell therapy manufacturing
- Regulatory Considerations



Product Life Cycle	Points for Consideration	Compliance Practices
Preclinical Research and IND Application	**Quality** ▪ Products must be appropriately characterized ▪ Quality must be ensured and maintained when it comes to research design; this requires accurate information on cell source, target indication, study dose and delivery method, animal model to be considered and population assays **Safety** ▪ The risks associated with the delivery procedure must be evaluated ▪ All *ex vivo* manipulation requirements must be identified ▪ All anticipated immune responses must be considered and accounted for ▪ The chances of teratoma / ectopic tissue formation must be estimated and assessed ▪ An assessment of cell migration to non-target regions must be carried out ▪ All interactions with concomitant therapies must be taken into account **Efficacy** ▪ Multiple parameters must be evaluated in the pharmacological and toxicological studies ▪ *In vitro* results must be appropriately evaluated ▪ All animal study results must be carefully assessed and taken into account, along with *in vitro* study data while estimating product efficacy	GLP
Clinical Trials	▪ Dosage requirements and duration of therapy must be optimized in the early phases ▪ Route of administration and anatomic site of delivery must be taken into account ▪ Eligibility criteria must be defined appropriately, such as the target patient population ▪ Several clinical parameters are assessed during the clinical studies; it is important that they are monitored carefully	GCP, cGMP, cGTP

Figure 8.1 Represents the regulatory considerations for cell therapies

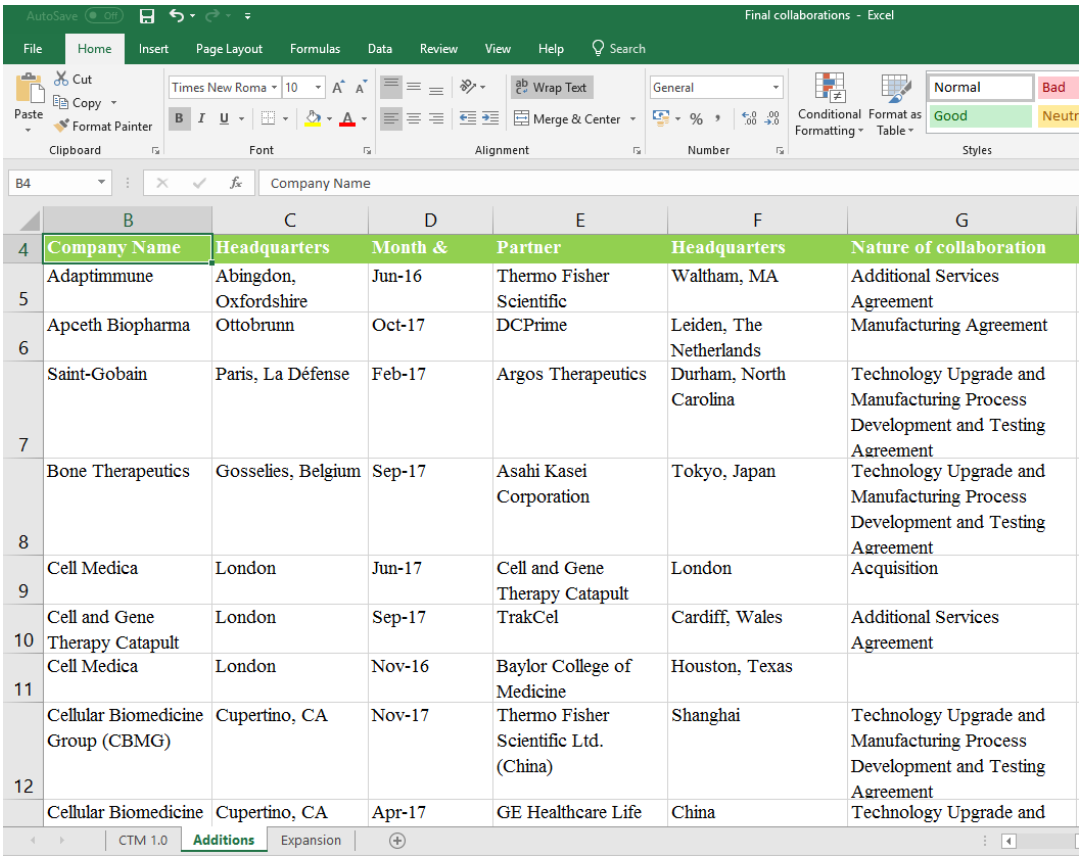
CHAPTER 9

RECENT DEVELOPMENTS

9.1Chapter Overview

This chapter presents insights on the various partnerships and collaborations related to cell therapy manufacturing that have been inked in the past few years.It also highlights the different types of partnership models that have been adopted by stakeholders in this domain and includes a comprehensive analysis of these partnerships based on various parameters. Overall, it provides an analytical overview of the activity of the various stakeholders in this evolving market.

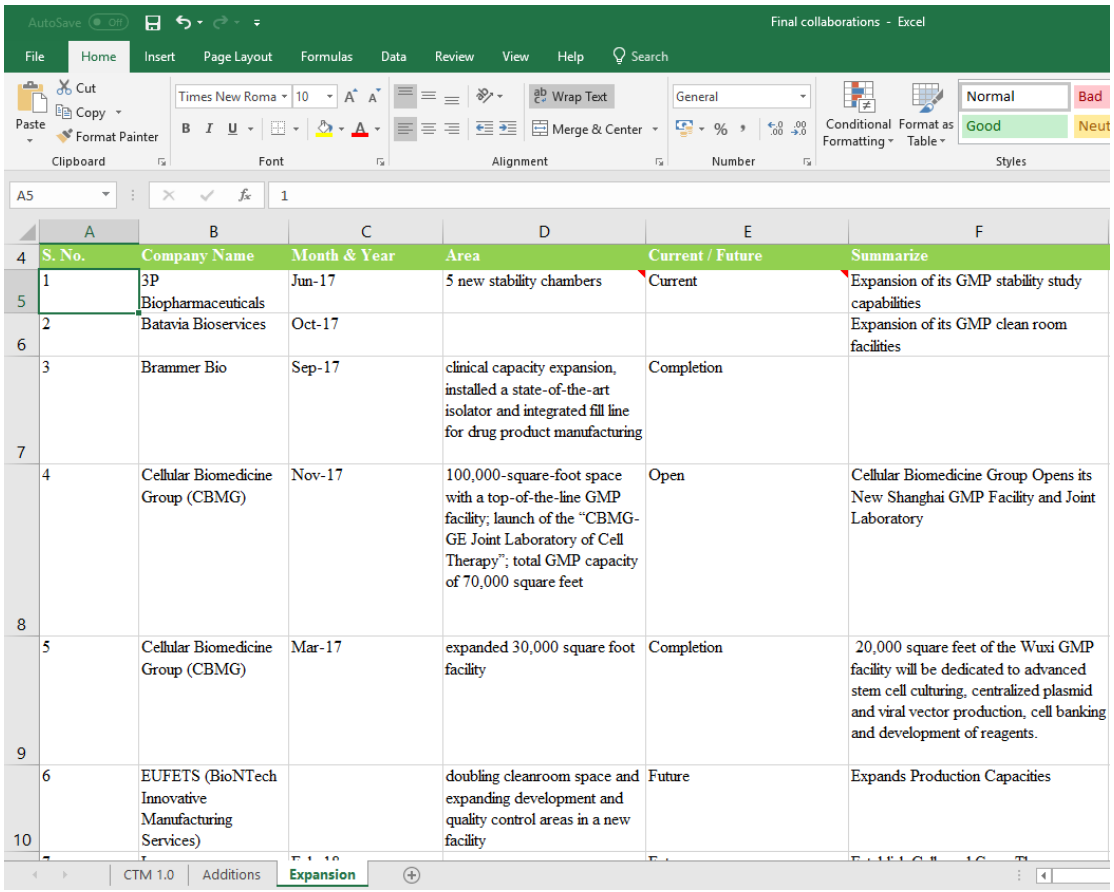
9.2 Partnerships



	B	C	D	E	F	G
4	**Company Name**	**Headquarters**	**Month &**	**Partner**	**Headquarters**	**Nature of collaboration**
5	Adaptimmune	Abingdon, Oxfordshire	Jun-16	Thermo Fisher Scientific	Waltham, MA	Additional Services Agreement
6	Apceth Biopharma	Ottobrunn	Oct-17	DCPrime	Leiden, The Netherlands	Manufacturing Agreement
7	Saint-Gobain	Paris, La Défense	Feb-17	Argos Therapeutics	Durham, North Carolina	Technology Upgrade and Manufacturing Process Development and Testing Agreement
8	Bone Therapeutics	Gosselies, Belgium	Sep-17	Asahi Kasei Corporation	Tokyo, Japan	Technology Upgrade and Manufacturing Process Development and Testing Agreement
9	Cell Medica	London	Jun-17	Cell and Gene Therapy Catapult	London	Acquisition
10	Cell and Gene Therapy Catapult	London	Sep-17	TrakCel	Cardiff, Wales	Additional Services Agreement
11	Cell Medica	London	Nov-16	Baylor College of Medicine	Houston, Texas	
12	Cellular Biomedicine Group (CBMG)	Cupertino, CA	Nov-17	Thermo Fisher Scientific Ltd. (China)	Shanghai	Technology Upgrade and Manufacturing Process Development and Testing Agreement
	Cellular Biomedicine	Cupertino, CA	Apr-17	GE Healthcare Life	China	Technology Upgrade and

Figure 9.1 Provides informationon collaborations / partnerships of key industry players

9.3 Expansions



S. No.	Company Name	Month & Year	Area	Current / Future	Summarize
1	3P Biopharmaceuticals	Jun-17	5 new stability chambers	Current	Expansion of its GMP stability study capabilities
2	Batavia Bioservices	Oct-17			Expansion of its GMP clean room facilities
3	Brammer Bio	Sep-17	clinical capacity expansion, installed a state-of-the-art isolator and integrated fill line for drug product manufacturing	Completion	
4	Cellular Biomedicine Group (CBMG)	Nov-17	100,000-square-foot space with a top-of-the-line GMP facility; launch of the "CBMG-GE Joint Laboratory of Cell Therapy"; total GMP capacity of 70,000 square feet	Open	Cellular Biomedicine Group Opens its New Shanghai GMP Facility and Joint Laboratory
5	Cellular Biomedicine Group (CBMG)	Mar-17	expanded 30,000 square foot facility	Completion	20,000 square feet of the Wuxi GMP facility will be dedicated to advanced stem cell culturing, centralized plasmid and viral vector production, cell banking and development of reagents.
6	EUFETS (BioNTech Innovative Manufacturing Services)		doubling cleanroom space and expanding development and quality control areas in a new facility	Future	Expands Production Capacities

Figure 9.2 Provides informationon expansion that the industry is undergoing for manufacturing of cell therapies

The collection of all these information on partnerships and expansions help the analyst to get an idea if the field is evolving or mature, research oriented or industry oriented and makes the report more impactful. It also helps the clients to identify potential collaborators and competitors and also allows researchers to focus on niche areas.

CHAPTER 10

PRIMARY RESEARCH

10.1 Overview

The data presented in the report has been gathered via secondary and primary research. For all the projects, we conduct interviews with experts in the area (academia, industry, medical practice and other associations) to solicit their opinions on emerging trends in the market. This is primarily useful for us to draw out our own opinion on how the market may evolve across different regions and technology segments. Wherever possible, the available data has been checked for accuracy from multiple sources of information.

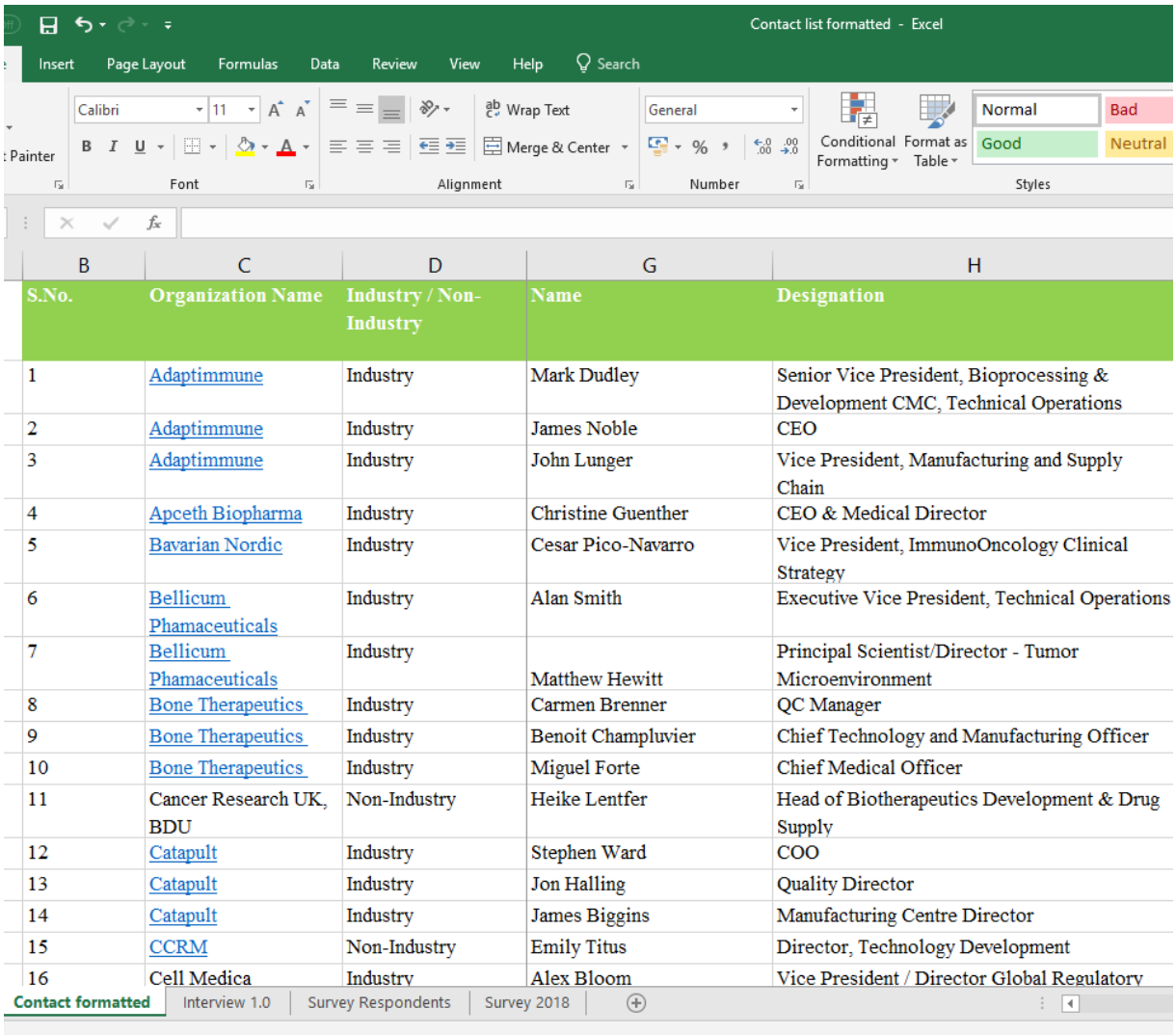
The interviews conducted with experts are scripted down and forms the important part of the project report. The information provided by the experts help a lot in validating the data as well as provide deeper insights of the project. For cell therapy manufacturing market project, we have conducted an interview with formula pharmaceuticals and scripted it down to present it in a form of a transcript in the report. In this process, the expert shares some key insights about the field and his opinion regarding the future market of the field. Once the discussion is over, a transcript is prepared that is send back to the expert for his permission and then after the transcript is included in the respective report.

10.2Interview Contacts

This was done to capture data that was to be used to conduct interviews with experts in this domain (academia, industry, medical practice and other associations). For this a database was prepared, including the contacts of all the main personnel of a company. Post gathering the desired data, interview requests were sent to the concerned person. These interviews form a part of primary research that is pivotal to have deeper insights of the project. Further, this information helps us to understand the emerging trends in

the market. Additionally, it aids in validating our own understanding of the domain, how the market is likely to shape up across different regions and technology segments in the coming future.

In addition, the contacts captured in the interview contact database / contact list were contacted and requested to respond to the survey which contained questions regarding the various manufacturing parameters. This exercise was a part of primary research and thus help us to understand the market in a much better way. We can also confirm and validate the parameters through the survey responses that were initially captured in the main database.



B	C	D	G	H
S.No.	Organization Name	Industry / Non-Industry	Name	Designation
1	Adaptimmune	Industry	Mark Dudley	Senior Vice President, Bioprocessing & Development CMC, Technical Operations
2	Adaptimmune	Industry	James Noble	CEO
3	Adaptimmune	Industry	John Lunger	Vice President, Manufacturing and Supply Chain
4	Apceth Biopharma	Industry	Christine Guenther	CEO & Medical Director
5	Bavarian Nordic	Industry	Cesar Pico-Navarro	Vice President, ImmunoOncology Clinical Strategy
6	Bellicum Phamaceuticals	Industry	Alan Smith	Executive Vice President, Technical Operations
7	Bellicum Phamaceuticals	Industry	Matthew Hewitt	Principal Scientist/Director - Tumor Microenvironment
8	Bone Therapeutics	Industry	Carmen Brenner	QC Manager
9	Bone Therapeutics	Industry	Benoit Champluvier	Chief Technology and Manufacturing Officer
10	Bone Therapeutics	Industry	Miguel Forte	Chief Medical Officer
11	Cancer Research UK, BDU	Non-Industry	Heike Lentfer	Head of Biotherapeutics Development & Drug Supply
12	Catapult	Industry	Stephen Ward	COO
13	Catapult	Industry	Jon Halling	Quality Director
14	Catapult	Industry	James Biggins	Manufacturing Centre Director
15	CCRM	Non-Industry	Emily Titus	Director, Technology Development
16	Cell Medica	Industry	Alex Bloom	Vice President / Director Global Regulatory

Figure 10.1 Highlights the various contacts of the key industry / non-industry players

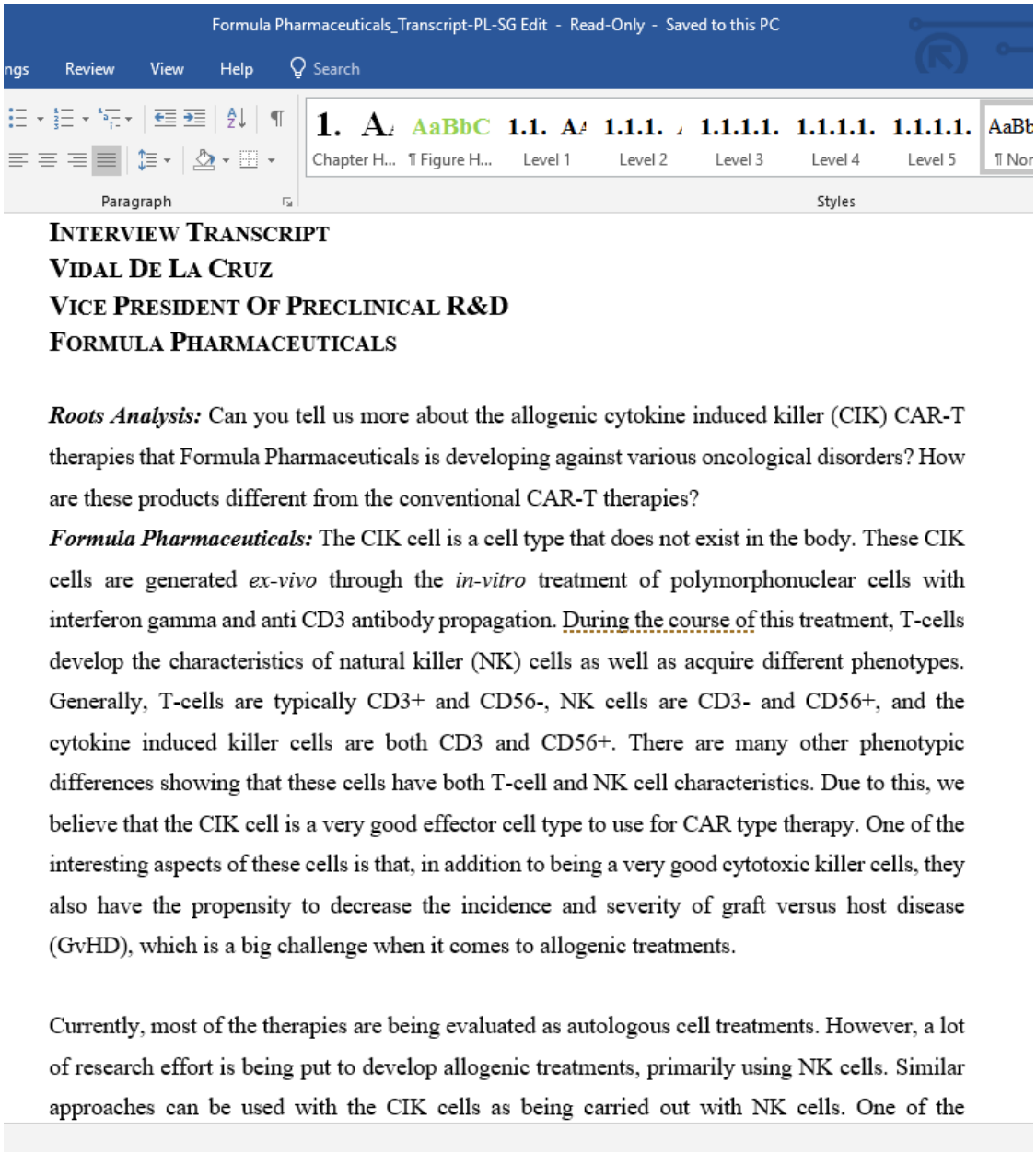


Figure 10.2 Represents the Interview Transcript for cell therapy manufacturing market project

CHAPTER 11

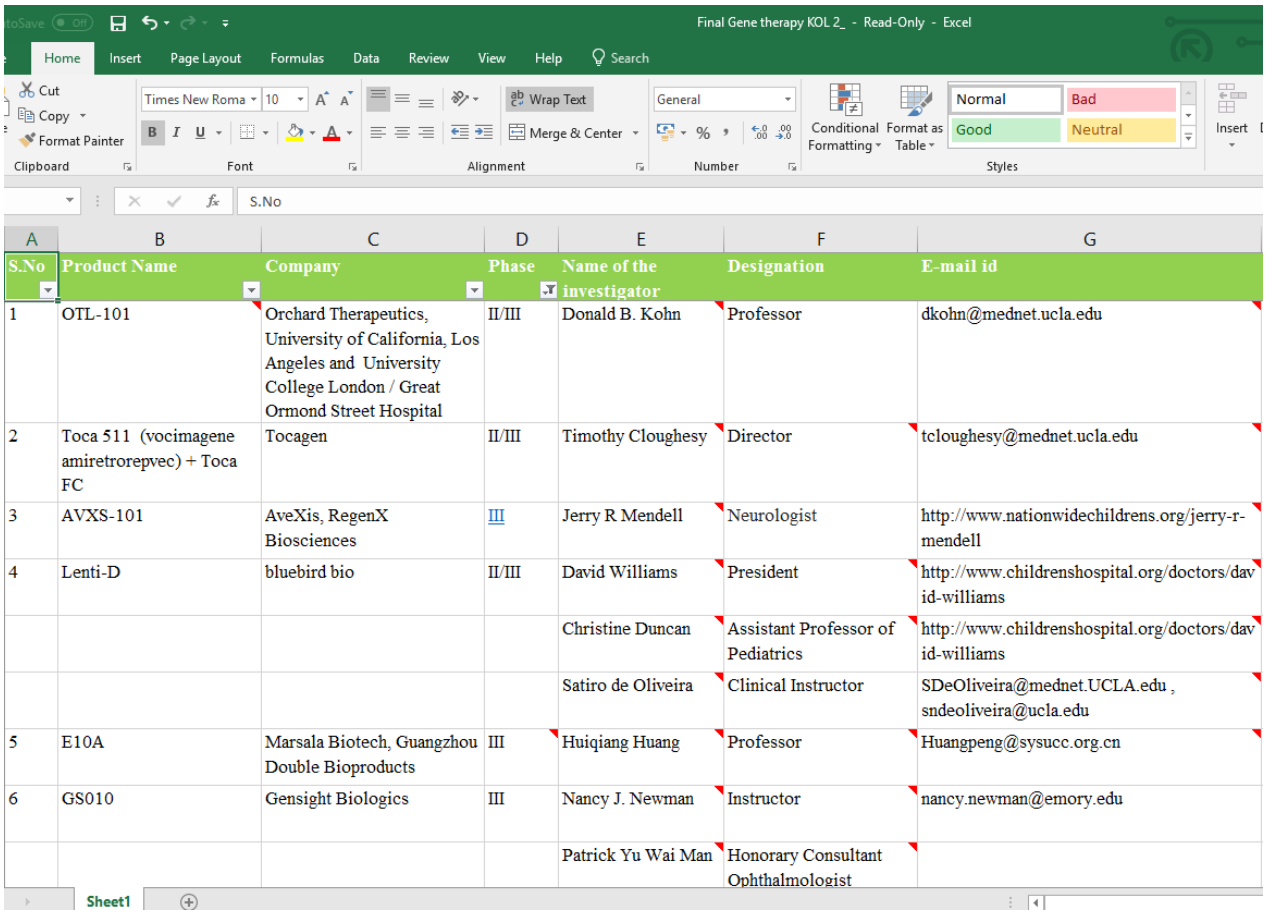
ADDITIONAL PROJECTS

11.1Gene Therapy

In addition to my project, I have also contributed in another project namely, Gene Therapy. Following section represents the work that I have been done in this project.

11.1.1Collecting KOLs

Mostly KOLs form a part of drug-based projects where information on key opinion leaders are collected which includes name of the company, product name, phase of the product,name of the investigator and their e-mail id's.



S.No	Product Name	Company	Phase	Name of the investigator	Designation	E-mail id
1	OTL-101	Orchard Therapeutics, University of California, Los Angeles and University College London / Great Ormond Street Hospital	II/III	Donald B. Kohn	Professor	dkohn@mednet.ucla.edu
2	Toca 511 (vocimagene amiretrorepvec) + Toca FC	Tocagen	II/III	Timothy Cloughesy	Director	tcloughesy@mednet.ucla.edu
3	AVXS-101	AveXis, RegenX Biosciences	III	Jerry R Mendell	Neurologist	http://www.nationwidechildrens.org/jerry-r-mendell
4	Lenti-D	bluebird bio	II/III	David Williams	President	http://www.childrenshospital.org/doctors/david-williams
				Christine Duncan	Assistant Professor of Pediatrics	http://www.childrenshospital.org/doctors/david-williams
				Satiro de Oliveira	Clinical Instructor	SDeOliveira@mednet.UCLA.edu , sndeoliveira@ucla.edu
5	E10A	Marsala Biotech, Guangzhou Double Bioproducts	III	Huiqiang Huang	Professor	Huangpeng@sysucc.org.cn
6	GS010	Gensight Biologics	III	Nancy J. Newman	Instructor	nancy.newman@emory.edu
				Patrick Yu Wai Man	Honorary Consultant Ophthalmologist	

Figure 11.1 Represents the list of Key Opinion Leaders engaged in the field of gene therapy

11.1.2Short Profiling of key industry players

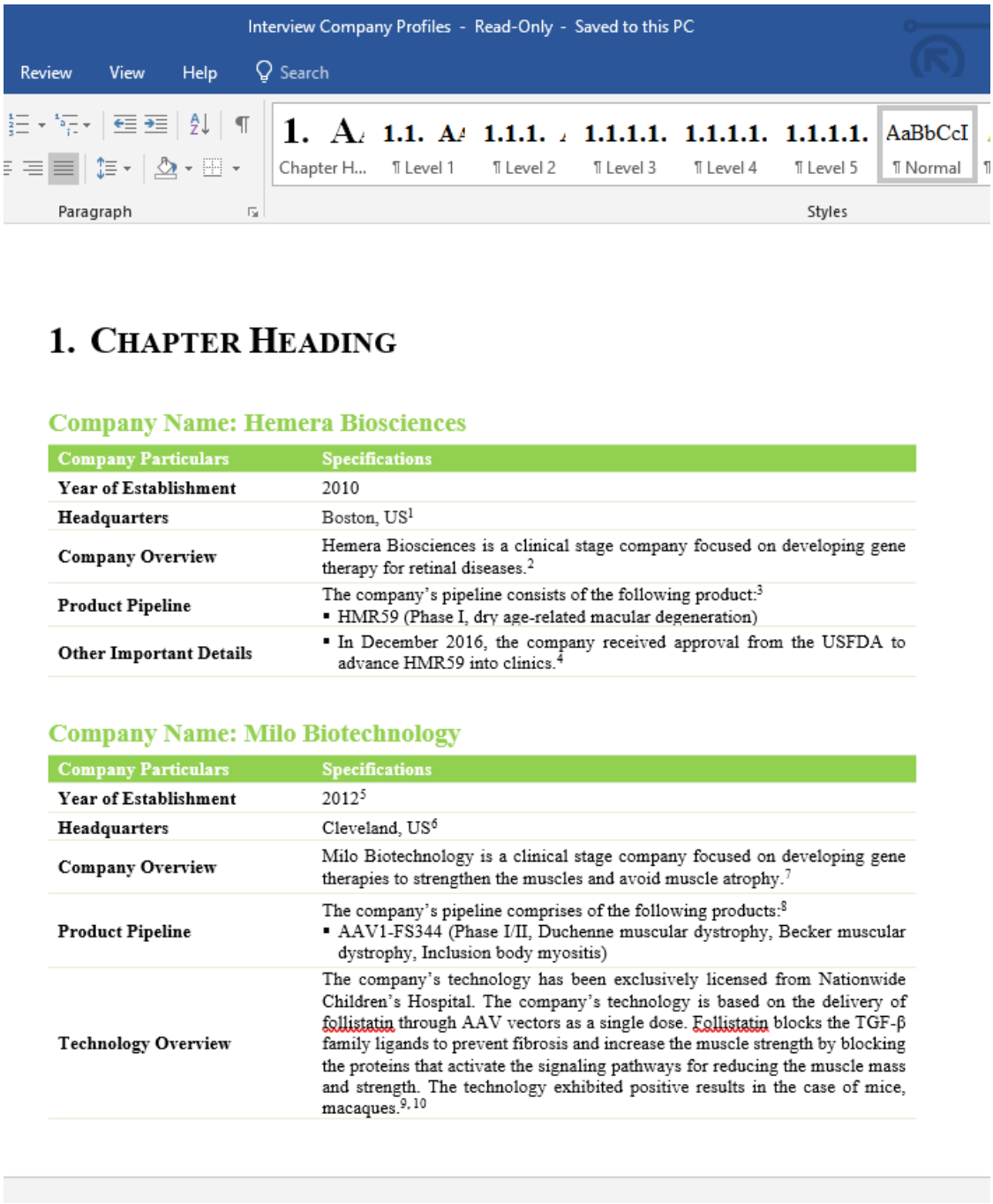


Figure 11.2 Represents the brief profiling of two industry players engaged in the field of gene therapy

11.2Undruggable Cancer Targets

In this project, I worked on two new representations:

11.2.1 Bulls Eye

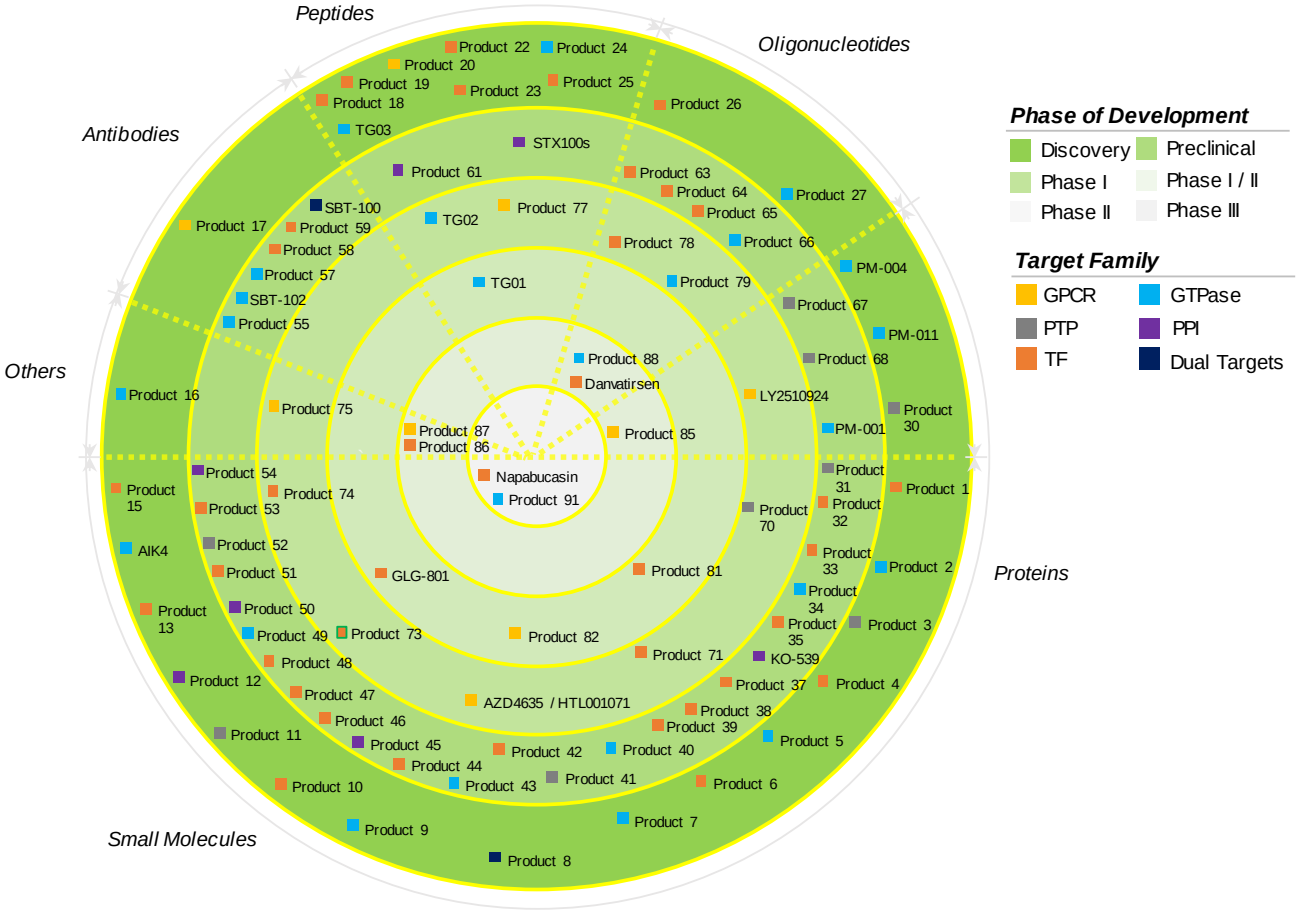


Figure 11.3 Bulls Eye Representation

11.2.2 Regional Analysis

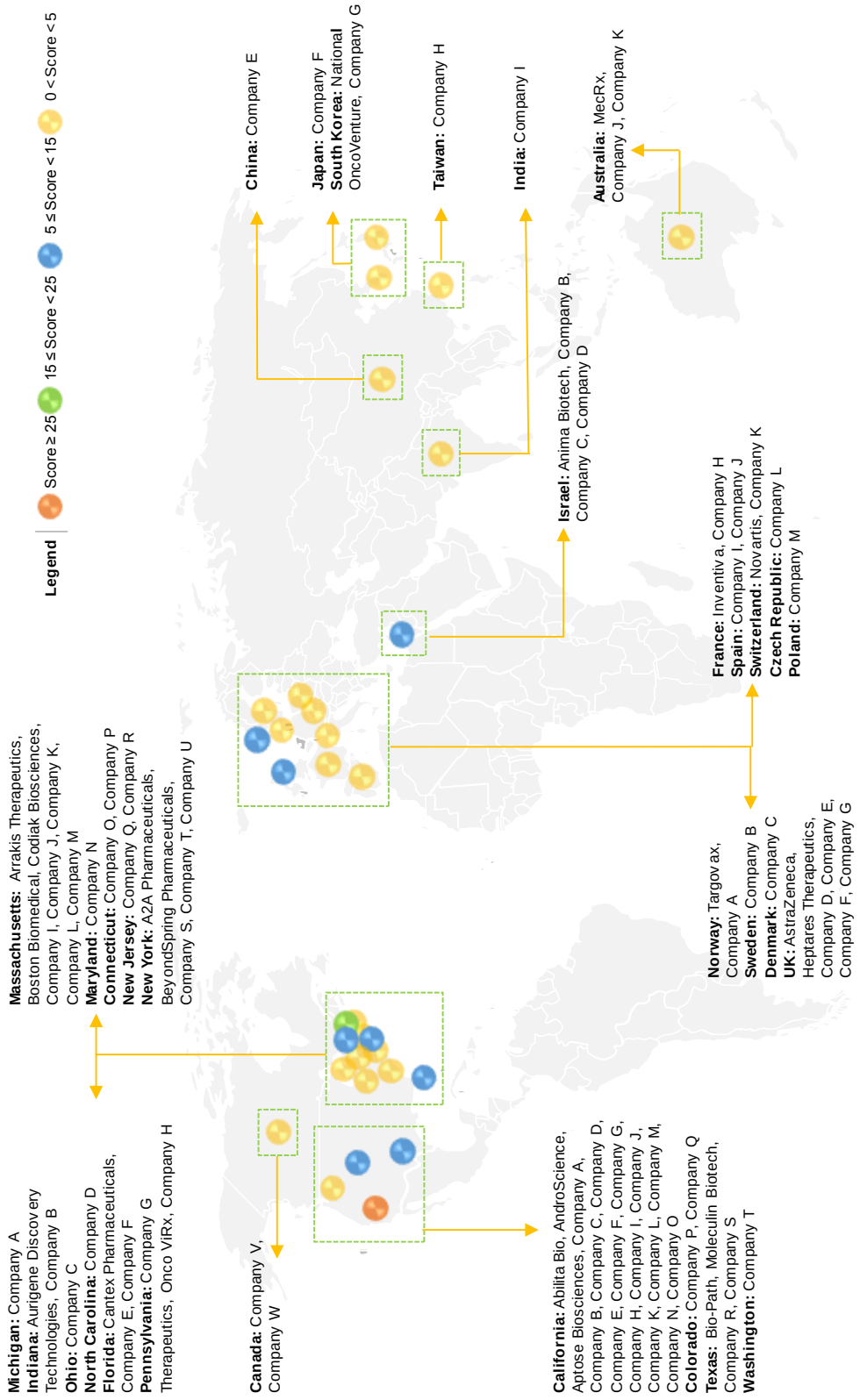


Figure 11.4 Regional Analysis

CHAPTER 12

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4. http://www.ac-gt.com/talks/pdfs/Manufacturing%20Cell%20and%20Gene%20Therapy%20Products%20-%20GE%20Healthcare.pdf
5. http://www.futuremedicine.com/doi/full/10.2217/rme.14.73
6. http://cellmanufacturingusa.org/sites/default/files/NCMC_Roadmap_021816_high_res-2.pdf
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